CONTROLLED TRIALS OF THE TREATMENT OF HÆMOLYTIC DISEASE OF THE NEWBORN*

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HERE is at present no general agreement about the tive value of different methods of treatment for nolytic disease of the newborn. This confusion ue to a failure to make valid comparisons between erent forms of treatment. Where comparisons have n attempted, they have been between groups of es treated not only by different methods but at erent periods of time. Inevitably there is doubt ether the cases that are compared are of equal erity and whether factors other than the type of nsfusion have operated to the same extent during period of observation.

he present paper records the results of controlled ils of treatment: that is to say, trials in which one e of treatment was given to approximately half infants in a series and another type to the remaining f, the treatment to be given being determined beforead by a system of chance. It is believed that, by this thod, closely comparable series have been obtained, d that the data provide the best available evidence the relative merits of the various forms of treatment hæmolytic disease of the newborn which are now being actised; in particular, they indicate unequivocally e value of exchange transfusion.

Exchange transfusion began to be practised in Britain 1947, doubtless mainly because of the description a simple and practical technique of performing the eration by the umbilical vein (Diamond 1947). At out the same time, many obstetricians began to actise premature induction of labour, a procedure which d also been recommended by Diamond (1947).

In 1948 a feeling arose that, owing to wide variations the severity of cases, the merits of these new forms of atment would be very difficult for any one person to . In order that sufficient material should be ilable for statistical analysis, it seemed desirable that eral centres should pool their cases. It was realised the outset that it would be essential to compare cases equivalent severity and that, to ensure this, treatment d probably have to be decided by random selection. At a preliminary meeting held in November, 1948, which 17 centres from the British Isles were represented, it was discovered that approximately half were rying out premature induction of labour as a routine asure, and that just over half were using exchange nsfusion rather than simple transfusion. The criteria for the selection of cases for exchange transfusion varied from centre to centre, and up to that time relatively few infants had been treated in this way.

Infants not treated by exchange transfusion were usually treated by simple transfusion for the relief of anæmia developing during the course of the illness, but in some centres it was the practice to give simple transfusions to most affected infants without waiting for the development of severe anæmia.

The Plan of the Trials

In the early part of 1949 a subcommittee put forward a definite scheme for trials, the essentials of which were as follows:

(1) It was to be a condition of taking part in the trials that each centre should either compare premature induction of labour with spontaneous delivery, or should compare exchange transfusion with simple transfusion, or should compare both.

(2) Treatment was to be decided not later than the 35th week of pregnancy, by opening an envelope which would contain instructions either regarding premature induction of labour or the type of transfusion to be given to the infant, or both. The instructions to be included in each envelope of the series were to be decided by a system of random numbers.

(3) Various tests were laid down for the detection of Rh antibody in the mother and for the detection of disease in the infant at birth. Special steps were taken to obtain comparable hæmoglobin estimations on cord-blood: the most important of these steps was the insistence that each centre should use the "M.R.C. Photometer" (King et al. 1948).

(4) Methods of carrying out treatment were carefully defined. For example, it was stipulated that, when labour was to be induced prematurely, induction should be performed between 35 and 21 days before the expected date of delivery; all transfusions were to be given within 9 hours of birth; when exchange transfusion was called for by the instructions, the amount of blood exchanged was not to be less than 60 ml. per lb. body-weight and a concentrated suspension of Rh-negative red cells was to be used. It was agreed that if the cord-blood hæmoglobin concentration exceeded 15·5 g. per 100 ml. no treatment need be given.

(Hb concentrations are abbreviated to "g." in this paper. Note that on the Haldane scale 15·5 g.=105%; 14·8 g.=100%; 11 g.=75%.)

In putting forward these "rules" it was emphasised that any centre which had a firm impression that one of these treatments was better than another could not take part in the scheme. As a result some withdrew, and it was interesting to note that these withdrawals were based on mutually contradictory impressions. Thus some centres felt that they could not abandon routine premature induction of labour, whereas others regarded premature induction as a purely experimental procedure which they were not willing to adopt. A few centres were unwilling to abandon exchange transfusion but many more felt unable to depart from simple transfusion, regarding exchange transfusion as hazardous and of doubtful benefit. However, a sufficient number of centres were left who were willing to try either premature induction of labour against spontaneous delivery, or to try exchange transfusion against simple transfusion, or both. The results that follow are all derived from centres where treatment was varied. Thus, for example, if a centre practised routine premature induction of labour but varied between simple and exchange transfusion, its results are used only in the "simple versus exchange transfusion" comparison and are not contrasted with those of another centre practising routine spontaneous delivery, to assess the relative methods of premature induction of labour and spontaneous delivery.

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he trials whose conclusions are briefly summarised here were conducted by a group of people, representing several different centres—namely: Prof. J. C. McC. BROWNE and Dr. P. L. MOLLISON (Hammersmith), Dr. W. A. B. CAMPBELL (Belfast), Dr. W. R. F. COLLIS and Dr. P. C. D. MACCLANCY (Rotunda), Miss DOREEN DALEY (St. Helier), Dr. R. J. DRUMMOND (Cardiff), Dr. D. M. T. GAIRDNER (Cambridge), Prof. W. F. GAISFORD (Manchester), Dr. JOHN MURRAY (Queen Charlotte's), Mr. S. D. PERCHARD and Dr. V. W. PUGH (Mile End), Dr. MARGARET M. PICKLES (Oxford), Dr. G. H. TOVEY (Bristol), and Dr. W. WALKER (Newcastle). The scheme was organised by the Blood Transfusion Research Unit of the Medical Research Council, with assistance from the Council's Statistical Research Unit at the London School of Hygiene and Tropical Medicine. A full report of the trials is at present being prepared. Meanwhile we are very grateful to our colleagues for empowering us to publish this preliminary report.

uring the tenure of a Luccock Research Fellowship.

Before finally deciding upon the rules there was some discussion about the type of treatment with which exchange transfusion should be compared. Two alternative treatments were considered:

(1) "Early simple" transfusion—i.e., the giving of a simple transfusion within a few hours of birth to any infant with a cord hæmoglobin of less than 15·5 g. per 100 ml.

(2) "Late simple" transfusion, that is, transfusion for the relief of anæmia, as and when it occurred.

The subcommittee finally decided to recommend "early simple" transfusion rather than "late simple" transfusion, feeling that if "late simple" transfusion was used and proved inferior to exchange transfusion, then it might still be said that exchange transfusion owed its superiority to the supply of some protective factors and that accordingly "early simple" transfusion might, if tried, be found as effective as exchange transfusion. Alternatively it might be held that "early simple" transfusion, by indirectly reducing the proportion of circulating Rh-positive red cells, might achieve much the same ends as exchange transfusion. It was therefore considered that a trial of exchange transfusion versus early simple transfusion would, in effect solve two problems. Firstly, it would show whether exchange transfusion was better than simple transfusion, and secondly, if exchange transfusion proved better, it would indicate clearly that this was due to the removal of the bulk of the infant's red cells rather than to some other effect.

One centre (N) felt strongly that it was more important to compare exchange transfusion with transfusion given solely to relieve anæmia rather than with routine "early simple" transfusion. It also considered that the cord-hæmoglobin level of 15·5 g. that was to decide the giving or withholding of transfusion was rather too high. The following modified plan was therefore adopted by this centre:

> Envelopes were opened only after birth and only if the cord-hæmoglobin concentration was less than 14·8 g. per 100 ml. (100% Haldane). When the instructions called for simple transfusion this was given only if the cord-hæmoglobin concentration was 11 g. or less, or if the hæmoglobin content subsequently fell below 11 g. At this centre there was no trial of premature induction and all women were allowed to go into labour spontaneously.

In the following analysis cases from centre N with cord-hæmoglobin concentrations of 11 g. or less are included in the comparison of exchange transfusion and "early simple" transfusion, since the treatment of these cases differed in no way from that used at other centres; the cases with cord-hæmoglobin concentrations exceeding 11 g. are considered separately, since in these simple transfusion was given only for the relief of anæmia. Although at this centre no envelopes were opened for infants whose cord hæmoglobin exceeded 14·8 g., since these infants received no early treatment, records were kept of all such infants born during the period of the trials and these cases are considered as part of the series from centre N.

Results

The following results are based on observation upon 477 infants with hæmolytic disease of the newborn, all of whom were born either at term or within 35 days of the expected day of delivery. (Cases born earlier have been excluded.) However, for the various comparisons made below only certain infants were suitable. For example, in comparing exchange transfusion with simple transfusion, infants with cord-hæmoglobin concentrations exceeding 15·5 g. per 100 ml. could not be used since such infants were not treated. However, if the same cases occurred in the "premature induction of labour versus spontaneous delivery" comparison, they could be used.

In this preliminary account the results of treatment have been expressed simply in terms of death or survival, and all infants living for one month or more have been considered as "living"; infants dying from causes other than hæmolytic disease have been included in the "dying." In the fuller account of the trials which is now being prepared, the question of cerebral damage in surviving infants will be considered.

COMPARISON OF PREMATURE INDUCTION AND SPONTANEOUS DELIVERY

Cases for this comparison were drawn only from centres which were carrying out both premature induction and spontaneous delivery according to instructions in sealed envelopes. Some of the centres were using only one form of transfusion treatment while others were varying exchange with early simple transfusion according to random numbers.

Table I refers only to cases in which the rules of the trial were strictly complied with: however, although the rules stated that premature induction of labour should be carried out between 35 and 21 days before the expected day of delivery, infants born 18 days or more before the expected day were included. Note that all infants born more than 35 days before the expected date of delivery, whether born alive or dead, were excluded from the investigation. In addition any case in which the infant was known to have died in utero more than 35 days before term was excluded, even if the mother was delivered within 35 days of term.

Table I shows that the practice of premature induction was associated with a reduced incidence of stillbirths but that this was outweighed by the increased incidence of neonatal deaths: hence the total death-rate, in the "induced" group is higher than in the group allowed to go to spontaneous delivery. The probability of obtaining a chance difference of this magnitude is 1 in 14, which, although not reaching the usually accepted significance level of 1 in 20, is none the less very suggestive. It can also be calculated from the findings that the odds are 39 to 1 against premature induction improving the survival-rate by more than 1%.

TABLE I—COMPARISON OF THE EFFECTS OF PREMATURE INDUCTION OF LABOUR AND SPONTANEOUS DELIVERY

Treatment	No. of cases	Living	Dying			Mortality
			Neonatal death	Still-birth	Total	
Induced ..	77	49	22	6	28	36·4%
Spontaneous..	108	82	12	14	26	24·1%

It will be noted that the number of cases in the "induced" group is considerably smaller than the number in the "spontaneous" group. The difference is accounted for by the exclusion of cases from the induced group due to failure to carry out premature induction of labour within the time-limits specified by the rules. Further analysis of the data suggests that the effect of these omissions is not serious.

COMPARISON OF EXCHANGE AND EARLY SIMPLE TRANSFUSION

Before giving the figures it must be emphasised that the results refer to cases of more than average severity. A large number of infants who had cord-hæmoglobin concentrations exceeding 15·5 g. (14·8 g. at centre N) received no treatment and are thus excluded from the present analysis; the great majority of these pursued a mild course, and they are considered separately below. The average severity of the cases was also substantially increased by including only those cases from centre N in which the cord hæmoglobin was 11 g. or less (see above). A few infants who were moribund at birth, and thus did not receive the intended treatment, were excluded. The figures in table II refer only to cases in which the rules for the trial were strictly complied with—e.g., exchange transfusion was carried out within

TABLE II—OVER-ALL COMPARISON OF EXCHANGE AND EARLY SIMPLE TRANSFUSION

—	Total	Living	Died
Exchange	62	54	8
Simple (early)	57	36	21

(p = 0·002.)

hours of birth. (Although the rules called for the exchange of 60 ml. of blood per lb. body-weight, only cases in which less than 50 ml. per lb. was used were in fact excluded.)

As table II shows, mortality was considerably lower in the group treated by exchange transfusion (13%) than in the group treated by simple transfusion (37%). As already emphasised, these figures do not indicate the mortality that would be expected in an ordinary consecutive series, for the cases treated are ones of more than average severity. It must also be remembered that a considerable proportion of the infants were immature.

A most informative comparison is obtained by dividing the cases, firstly according to maturity, and secondly according to whether the cord-hæmoglobin concentration did or did not exceed 11 g. This shows that the significance of the over-all difference between exchange transfusion and simple transfusion is due entirely to two of the four groups—namely, immature infants with cord-hæmoglobin concentrations exceeding 11 g., and full-term infants with cord-hæmoglobin concentrations equal to, or less than, 11 g. In full-term infants with hæmoglobin concentrations exceeding 11 g. the survival-rate is high with both simple and exchange transfusion, and in premature infants with cord-hæmoglobin concentrations of 11 g. or less the survival-rate is rather low with both treatments.

It seemed possible that cases excluded owing to non-compliance with the rules might be ones with a worse-than-average prognosis. Accordingly, a second analysis was made, including cases under their intended treatments, whether or not they actually received them. This analysis did not modify to any important extent the conclusions which have already been stated.

COMPARISON OF EXCHANGE AND "LATE SIMPLE" TRANSFUSION

The cases upon which this comparison is based are all drawn from a single centre (N) and consist only of infants whose cord hæmoglobin was between 11·1 and 14·8 g. per 100 ml. When the instructions were for exchange transfusion, this was carried out within 9 hours of birth, as usual. However, when the instructions were for simple transfusion, treatment was withheld unless the hæmoglobin concentration of a skin-prick sample subsequently fell below 11 g. Thus, 7 cases selected for simple transfusion never received any treatment; of these, 4 survived, while 3 died with kernicterus.

3 infants with cord-hæmoglobin values of over 11 g. were treated by simple transfusion on the first day of life, 1 because of bleeding from the cord and 2 because of a misunderstanding about the cord-hæmoglobin value: 2 of these infants survived while the other died with kernicterus. All 3 are excluded from the present comparison.

Table III shows a suggestive but not significant difference in favour of exchange transfusion as compared with simple relief of anæmia. The death-rates are not significantly different from those for similar groups included in the comparison of exchange transfusion and early simple transfusion—namely, mature infants with cord-hæmoglobin concentrations between 11·1 and 15·5 g.

TABLE III—COMPARISON OF EXCHANGE TRANSFUSION AND "LATE SIMPLE" TRANSFUSION IN INFANTS WITH CORD-HÆMOGLOBIN CONCENTRATIONS BETWEEN 11·1 AND 14·8 G.

—	Total	Lived	Died
Exchange	24	24	0
Late simple	23	20	3

RESULTS FROM CENTRE N CONSIDERED ALONE

The results from centre N are of special interest because they form by far the largest group treated at a single centre. In the above analysis, as explained, they have been split up, because those due for simple transfusion received the transfusion "early" or "late," depending upon the cord-hæmoglobin concentration. However, they may be considered together and then form two parallel series: (*a*) treated by exchange transfusion; (*b*) treated by simple transfusion only if and when they were anæmic.

Of 44 infants treated by exchange transfusion 43 survived, whereas in 40 infants treated by simple transfusion only 29 survived. (p < 0·001.)

All the infants in this series were born spontaneously and only 4 were premature (birth weight 5½ lb. or less). By chance all 4 of these infants were treated by simple transfusion and 3 died, all with kernicterus. Even if these 4 infants are excluded from the analysis, the figures for exchange transfusion remain significantly better than those for simple transfusion. (p = 0·009.)

INFANTS WITH CORD-HÆMOGLOBIN CONCENTRATION EXCEEDING 15·5 G. (14·8 G. AT CENTRE N)

Of the 191 infants in this group none received transfusion during the first few days of life, though 24 of the 177 survivors did in fact become sufficiently anæmic during the first month of life to need transfusion.

The 191 cases have been divided into two groups: those born less than 18 days before the expected day of delivery ("full-term"); and those born between 18 and 35 days before the expected day of delivery ("immature"). The outcome in these cases is shown in table IV. Note that the mortality was about 1 in 7 in immature infants but only 1 in 20 in full-term infants.

TABLE IV—ANALYSIS OF DEATHS IN INFANTS WITH CORD-HÆMOGLOBIN CONCENTRATIONS OVER 14·8 G.

—	Cord-Hb concentration 14·9–17·5 g.		Cord-Hb concentration 17·6–21·5 g.	
	Total	No. of deaths	Total	No. of deaths
Full-term	111	6 (5 kernicterus; 1 other cause)	40	1 (other cause*)
Immature	28	6 (4 kernicterus; 2 other cause)	12	1 (other cause)

* "Other cause" means death from a cause apparently unrelated to hæmolytic disease of the newborn, such as asphyxia.

If the cases are divided by birth weight rather than by length of gestation, a still more striking contrast results. Thus, taking only infants with cord-hæmoglobin concentrations between 14·9 and 17·5 g., amongst 11 infants weighing 5½ lb. or less there were 3 deaths (all from kernicterus) whereas amongst 128 infants weighing more than 5½ lb. there were 9 deaths (6 from kernicterus). In these selected groups mortality was thus about four times as high in premature infants as in mature infants.

CAUSES OF DEATH

Out of a total of 477 Rh-positive infants born at term, or within 35 days of term, 24 were stillborn. Among the remaining 453 infants born alive there were 79 deaths within the first week of life.

Amongst the 79 infants dying during the first week of life the cord-hæmoglobin concentration was estimated in all but 5 cases: in these 5 cases death occurred within half an hour of birth in one instance, and at 3–7 days in the remaining 4: in at least 1 of these 4 latter cases death was due to kernicterus.

14 deaths occurred in infants whose cord-hæmoglobin concentration exceeded 15·5 g., and these have already been described: 9 were thought to be due to kernicterus and occurred between the 2nd and 6th days of life; 5 were thought to be due to other causes and 4 of these deaths occurred on the 1st day of life.

There remain 60 deaths to describe, all of which occurred in infants whose cord-hæmoglobin concentration was less than 15·5 g. Of those, 9 infants were moribund at birth; all had hæmoglobin concentrations below 7·4 g. (50% Haldane). A further 8 died within 18 hours of birth. These 8 deaths occurred amongst a total of 188 infants who received transfusion (either exchange or simple) within 9½ hours of birth. All these 8 infants were severely anæmic at birth (cord-hæmoglobin concentration below 8·8 g.) and 4 had definite signs of cardiac failure at necropsy. It was noteworthy that in the 2 cases in which death occurred within 18 hours of an exchange transfusion, the infant had been injected with 40 ml. more of blood than was withdrawn. It has been emphasised elsewhere that in infants with hæmolytic disease of the newborn severe anæmia at birth is usually accompanied by a raised venous pressure and that in performing exchange transfusion in these cases it is advisable to withdraw more blood than is injected (Mollison and Cutbush 1949, Mollison 1951).

Of the remaining 43 deaths, all of which occurred between 1 and 6 days after birth, 36 were considered to be due to kernicterus. In some cases the diagnosis of kernicterus was made from clinical signs although in the majority a post-mortem examination was made and the diagnosis based on the finding of yellow staining of the basal ganglia. The remaining 7 deaths were ascribed to such causes as intracerebral hæmorrhage and asphyxia, although in some instances kernicterus was not definitely excluded as a contributory cause.

It is noteworthy that the high death-rate in infants treated by simple transfusion was due entirely to a far higher incidence of fatal kernicterus. Thus, taking the groups set out in table II, among 57 infants treated by early simple transfusion, there were 21 deaths, 18 of which were due to kernicterus; among 62 infants treated by exchange transfusion there were 8 deaths, 4 of which were due to kernicterus. Thus the incidence of fatal kernicterus was about five times higher in infants treated by simple transfusion than in infants treated by exchange transfusion. It must also be emphasised that in 4 infants who developed fatal kernicterus despite exchange transfusion, 3 were premature (birth weight 5½ lb. or less); thus the present experience does not conflict with the claim that the incidence of fatal kernicterus in mature infants treated by exchange transfusion is negligible (Allen et al. 1950b).

SUBSEQUENT PROGRESS OF INFANTS

Out of 374 surviving Rh-positive infants, 368 were examined at the age of 1 month and assessed as normal or abnormal. The intention was to detect infants with signs of damage to the central nervous system and the presence of anæmia or jaundice at this age was not regarded as abnormal for the present purpose. Out of 368 infants only 13 (3·6%) appeared to have signs of damage to the central nervous system.

The full report to be published later will deal with examinations at the age of 6 months and, if possible, at 1 year. Results analysed so far suggest that not more than 5% of the surviving infants will be recognisably abnormal.

Discussion

The practice of inducing labour 3–5 weeks before the expected day of delivery, as a routine, in women whose serum contained Rh antibody, was associated with a lower incidence of surviving infants than was t practice of allowing labour to occur spontaneously Although this reduction in the survival-rate, followi premature induction of labour, was small (about 10% and could have been due to chance, it can be calculated that further trials would be very unlikely to show that the practice of premature induction actually increases the survival-rate.

Since it appears certain that any advantage that the affected (Rh-positive) infant derives from premature induction of labour is at the most small, the disadvantage to the mother cannot be ignored. Moreover, the unnecessary hazard to which occasional Rh-negative infants are exposed by premature induction of labour must be considered. These factors will be discussed in the full report of the trials.

The present investigation shows beyond reasonable doubt that infants treated by exchange transfusion have a greater chance of survival than infants treated by simple transfusion. Further analysis of the results shows that the improvement produced by exchange transfusion can be clearly demonstrated only in two main groups of cases—namely, mature infants who are severely affected (cord-hæmoglobin concentrations 11 g. or less) and immature infants who are only moderately affected (cord-hæmoglobin concentrations above 11 g.). In mature infants who were only moderately affected the mortality following "early simple" transfusion was about as low as it was after exchange transfusion. It is apparent that if a series consisting mainly of such infants were treated by simple transfusion, mortality would be low and it would be concluded that simple transfusion was a very satisfactory treatment (see, for example, Pennell 1950).

Immature infants who are severely affected (cord-hæmoglobin concentration 11 g. or less) have a low recovery-rate even when treated by exchange transfusion. Since many hospitals began the practice of premature induction of labour at the same time that they began to practise exchange transfusion, it is easy to see why mortality has sometimes remained disappointingly high.

The superiority of exchange transfusion over "earl simple" transfusion is most striking in immature infan who are only moderately affected. It is possible that the results of exchange transfusion seemed particularly favourable to Diamond (1947) because he had been practising premature induction of labour for some time before he began to use exchange transfusion. It should be added that his group was the first to realise that premature infants are far more likely than mature infants to develop kernicterus (Allen et al. 1950a) and that the infant's best chance of survival lies in not being born prematurely and being treated by exchange transfusion (Allen et al. 1950b).

The present results provide very useful data for examining the relationship between the cord-hæmoglobin concentration and the chance of survival with various treatments; this question will be considered in the full report of the trials. The only point to be emphasised here is that the curve published previously relating cord-hæmoglobin concentration to the chance of survival in infants treated by exchange transfusion (Mollison and Cutbush 1951) referred to a group of infants many o whom were immature. It has now become clear that the chance of survival following exchange transfusion is higher in mature infants than in immature infants. Indeed, mortality in mature infants treated by exchange transfusion is so low that it may prove difficult to construct a curve relating hæmoglobin concentration to survival in this group.

INDICATIONS FOR EXCHANGE TRANSFUSIONS

The present results indicate clearly that an immature infant affected with hæmolytic disease of the newborn whose cord-hæmoglobin concentration is below about

5 g. will be more likely to survive if it is treated by exchange transfusion. Although in the present series immature infants with cord-hæmoglobin concentrations above about 15 g. were not treated, the incidence of fatal kernicterus was as high as 1 in 12, and it seems extremely likely that this incidence could have been reduced to a low level by exchange transfusion. There was no case of kernicterus among the 12 affected immature infants with cord-hæmoglobin concentrations exceeding 17·5 g. (118% Haldane).

In severely affected mature infants exchange transfusion is again clearly the best treatment. In mature infants with cord-hæmoglobin concentrations between 1 and 15 g., "early simple" transfusion appeared to be as successful as exchange transfusion—although there was some suggestion that "late simple" transfusion gave worse results. Despite the failure to demonstrate any clear superiority of exchange transfusion in these cases, there seems little doubt that it is in fact superior. In mature affected infants with cord-hæmoglobin concentrations between 15 and 17·5 g. no treatment was given and the incidence of fatal kernicterus was about 1 in 21. In this group there are considerable differences between one infant and another and the problem is to detect those few infants who are going to become deeply jaundiced and be at risk from kernicterus. It is suggested that if a woman has previously lost an infant from hæmolytic disease of the newborn, it is always wise to treat the succeeding infant, however mildly it appears to be affected. Other indications will be discussed in the full report of the trials. Mature affected infants with cord-hæmoglobin concentrations over 17·5 appear to have so small a chance of developing kernicterus that treatment is not justified.

Since exchange transfusion will probably be practised increasingly in the future, it seems necessary to emphasise that the present trials have shown that, though highly experienced centres have no difficulty in performing successfully a series of exchange transfusions, centres with only small experience shared between frequently changing clinicians may sometimes fail to complete an exchange transfusion. Moreover in very ill infants the chance of survival following exchange transfusion is undoubtedly related to the way in which the procedure is carried out. It is of the first importance that a woman expected to give birth to an infant with hæmolytic disease of the newborn should be delivered in one of a limited number of institutions capable, by virtue of their experience, of maintaining a high degree of technical efficiency in the conduct of exchange transfusion.

Summary

1. Controlled trials of treatment of hæmolytic disease of the newborn were carried out in Britain from 1949 to 1951, the treatment to be given in any individual case being determined by a system of random numbers.

2. The practice of inducing labour 3–5 weeks before the expected day of delivery was associated with a lower proportion of surviving infants than was the practice of allowing delivery to occur spontaneously, though the difference did not quite reach the conventional level of significance.

3. Exchange transfusion was followed by a significantly higher survival-rate than was simple transfusion, both treatments being carried out equally early after birth. The incidence of kernicterus after exchange transfusion was very low.

4. Indications for exchange transfusion are discussed briefly, in the light of experience gained in these trials.

We should like to acknowledge our debt to Miss Marie Cutbush of the Blood Transfusion Research Unit for carrying out the laborious task of abstracting relevant information from all the record cards and tabulating it; to Dr. J. A. Fraser Roberts for advice in planning these trials; and to Dr. P. Armitage of the M.R.C. Statistical Research Unit for performing all the statistical tests and giving most valuable advice on the analysis of the data.

REFERENCES

Allen, F. H. jun., Diamond, L. K., Vaughan, V. C. (1950a) *Pediat.* 6, 441.
— — — (1950b) *Amer. J. Dis. Child.* 80, 779.
Diamond, L. K. (1947) *Proc. R. Soc. Med.* 40, 546.
King, E. J., Wootton, I. D. P., Donaldson, R., Sisson, R. B., Macfarlane, R. G. (1948) *Lancet,* ii, 971.
Mollison, P. L. (1951) Blood Transfusion in Clinical Medicine. Oxford.
— Cutbush, M. (1949) *Brit. med. J.* i, 123.
— — (1951) *Blood,* 6, 777.
Pennell, S. (1951) *Ibid.* 5, 107.

THE USE OF INTRATHECAL AUREOMYCIN IN MENINGITIS

METHODS OF OBTAINING BACTERIOSTATIC CONCENTRATIONS OF AUREOMYCIN IN THE CEREBROSPINAL FLUID

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Most kinds of purulent meningitis can now be controlled with sulphonamides, penicillin, or streptomycin. There remains, however, the occasional case in which the causal organism is resistant to these drugs. The need for some effective method of treating such cases is urgent because, though not numerous, they are usually fatal. Moreover, now that intrathecal medication and anæsthesia are so widely practised, their number is increasing, and with it the need for alternative forms of chemotherapy. The question naturally arises whether aureomycin, so useful in the treatment of systemic infections, can help to fill this dangerous gap in our treatment of meningitis.

PASSAGE OF AUREOMYCIN FROM BLOOD TO CEREBROSPINAL FLUID

Some success has been reported from the systemic administration of aureomycin in meningitis due to *Hæmophilus influenzæ* (Drake et al. 1950), pneumococcus (Dowling et al. 1949), *Streptococcus fæcalis* (Schoenbach 1949), and *Bacterium coli* (Harvey et al. 1949), but the success of any antibiotic in the treatment of meningitis depends on whether or not an effective concentration of the drug can safely be set up and maintained in the cerebrospinal fluid (C.S.F.). Dowling et al. found disappointingly low concentrations of aureomycin in the C.S.F. during systemic administration (0·25 µg. per ml.), while in those successful cases in which the in-vitro sensitivity of the organism to aureomycin was stated it was very high. The sensitivity of most other organisms, including those for which aureomycin is particularly needed, such as penicillin-resistant staphylococci, *Pseudomonas pyocyanea, Bact. aerogenes, Salmonella aertrycke,* and micrococci, usually falls well outside this range. The effect of systemic administration will be correspondingly disappointing, as in the following case:

Case 1.—A girl, aged 20, developed a subdural abscess and leptomeningitis after hemispherectomy (Cairns and Davidson 1951). Both the pus from the abscess and the lumbar C.S.F. grew *Bact. aerogenes* on culture. This organism was resistant in vitro to both penicillin and streptomycin and was inhibited only by aureomycin 2·5 µg. per ml. Full doses of sulphonamides failed to control the infection. She was then given aureomycin 3 g. daily by mouth, but grew steadily worse, and no more than 0·05 µg. per ml. could be detected in the C.S.F. As her condition was now desperate, it was decided to put aureomycin directly into the abscess cavity. The only preparation then available to us was

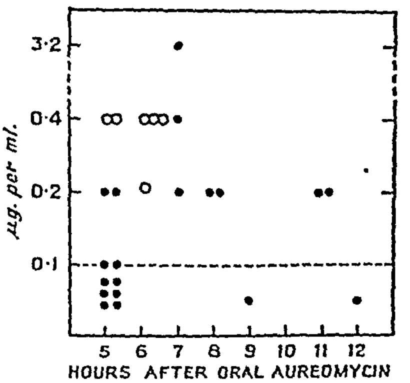
TABLE I—SOME EXAMPLES OF THE FALL IN BLOOD-PRESSURE AFTER SYSTEMIC AUREOMYCIN

Patients	Dose of aureomycin (g.)	Resting blood-pressure (mm. Hg)	*Blood-pressure after administration of aureomycin (mm. Hg)*								
			1 hr.	4 hr.	6 hr.	8 hr.	12 hr.	24 hr.	48 hr.	4 days	5 days
N. F. (aged 60)	4	220/130	180/120	140/105	..	..	140/80	160/110	220/110	..	..
W. G. (aged 63)	4	210/120	..	..	145/100	140/90	190/110	230/120	..	..	..
B. M. (aged 59)	4	210/130	..	..	200/125	..	130/90	145/90	190/100	..	..
S. H. (aged 69)	2	210–300/100	..	..	..	..	135/80	135/80	140/80	(discharged)	
A. H. (aged 60)	500 mg. i.v.	190/100	..	..	125/70	..	..	155/85	..	160/90	190/100

Lederle's aureomycin in a leucine buffer (pH 9) for intravenous use. This was injected into the abscess cavity, and a concentration of up to 50 µg. per ml. was maintained in the cavity. *This controlled the source of infection,* and the patient recovered, although the amount of aureomycin in the C.S.F. was only 0·1 µg. per ml.

Systemic aureomycin failed to control this infection, both in the abscess and in the meninges. In retrospect the risk of putting an unsuitable substance into the cerebrospinal pathways was justified by the brilliant success of the local treatment. It was clear, therefore, that aureomycin could be extremely useful, provided a method could be devised for establishing therapeutic levels in the C.S.F.

The failure of aureomycin to pass from the blood to the C.S.F. in adequate amounts was confirmed by observations made on neurosurgical patients whose treatment entailed repeated spinal punctures. Before their punctures, aureomycin was given by mouth to 10, and intravenously to 5, patients. This was done partly as a chemotherapeutic cover for surgical operations, and partly so that the passage of aureomycin from blood to C.S.F. might be observed. By mouth aureomycin 1–4 g. was given in three hours, except in the case of a child, aged 2½ years, who received 0·5 g. Intravenous aureomycin was given as a single dose of 200–500 mg. The aureomycin levels in the blood and C.S.F. were estimated at intervals by the doubling dilution method recommended by Lederle's laboratories using a sensitive strain of *Bacillus cereus.* The blood-aureomycin level usually rose to 4–8 µg per ml. The C.S.F.-aureomycin levels after oral aureomycin are shown in the accompanying figure: levels below 0·1 µg. per ml. are not significant and are therefore only recorded as below this level. The samples were obtained between the fifth and twelfth hours. At the fifth hour 6 of the 10 specimens of lumbar C.S.F. contained less than 0·1 µg. of aureomycin per ml. and only 2 contained as much as 0·2 µg. of aureomycin per ml.; whereas between the seventh and twelfth hours 7 of the 9 specimens contained 0·2 µg. or more of aureomycin per ml. In 2 cases (one in a patient who had had 4 g. of aureomycin) the lumbar C.S.F. did not contain more than traces of aureomycin, although the blood-aureomycin levels were 4 µg. per ml. and 8 µg. per ml. On the other hand, one patient who had had only 2 g. of aureomycin had a blood-aureomycin level of 32 µg. per ml. and a C.S.F.-aureomycin level of 3·2 µg. per ml. at the same time.



Lumbar and ventricular C.S.F.-aureomycin levels after oral aureomycin: solid circles, lumbar, open circles, ventricular.

Ventricular as well as lumbar C.S.F. was obtained at operation from 6 of these 10 patients. In 5 of these the ventricular C.S.F.-aureomycin level was 0·4 µg. per ml., and in each case it was more than in the lumbar C.S.F.

Intravenous administration was even less satisfactory. The blood-aureomycin levels were of the same order as those obtained after oral administration, but the C.S.F.-aureomycin levels were lower. In 2 of the 5 patients the aureomycin levels in the lumbar C.S.F. did not reach 0·1 µg. per ml. The highest C.S.F.-aureomycin levels in the other 3 patients were reached at the fourth hour: 0·2 µg. per ml. in 1 case and 0·1 µg. per ml. in the 2 others.

In conclusion, it was found impossible to obtain a therapeutic C.S.F.-aureomycin level by giving aureomycin systemically. It was therefore clear that effective levels could be reached only if aureomycin could be given intrathecally.

SIDE-EFFECTS

We noticed two side-effects of systemic aureomycin which have not to our knowledge been reported before. First, in hypertensive patients the blood-pressure fell, sometimes even to normal levels. This observation was later confirmed in several other hypertensive patients outside this series. The effect was sometimes profound (e.g., from 220/130 to 140/80 mm. Hg), and usually lasted up to forty-eight hours, but in 2 cases it lasted longer (table I). Secondly, whenever observations were made, a definite, sometimes a very considerable, fall in the lumbar C.S.F. pressure was recorded. This fall in C.S.F. pressure was unrelated to a fall in systemic blood-pressure, since it was seen also in patients who were not hypertensive and in whom the blood-pressure was unaffected.

INTRATHECAL AUREOMYCIN

Preparation of Solution

Aureomycin is soluble as its hydrochloride (pH 2·6) or as its sodium salt (pH 10) but is precipitated in the pH range 5–9. The only soluble preparation we possessed was aureomycin in a leucine buffer at pH 9. As this solution, when used intravenously, was known to cause thrombophlebitis it was clearly unsuitable for intrathecal use.* For this reason one of us (K. A. W.), in conjunction with Mr. G. Higgins, of the department of biochemistry, prepared a solution containing aureomycin 0·5 mg. per ml. at pH 7 and of standard antibacterial activity.

The aureomycin was dissolved in a solution of 2% glycine in distilled water, and 0·3 ml. of N.NaOH was added to each 100 mg. of aureomycin. Full details are not given, because this preparation has since been modified by dissolving 100 mg. of aureomycin hydrochloride in 10 ml. of sterile distilled water. This solution has a pH of 2·6. It can be kept frozen solid without loss of antibacterial activity for at least six weeks. Immediately before use 1 ml. is added to 9 ml. of the buffering solution, which consists of a mixture of 9 ml. of 2% glycine in distilled water and 0·175 ml. of N/5 sodium hydroxide. The final solution has a pH of 7·2–7·4, contains 1 mg. of aureomycin per ml., and remains active for at least an hour. There may be a slight precipitate. The alkaline glycine mixture can be made up in bulk and distributed into rubber-capped vaccine bottles in amounts of 9 ml. These may be autoclaved and will keep without deterioration for at least six weeks.

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* The current preparation of intravenous aureomycin glycinate is said not to cause thrombophlebitis.

Preliminary Experiments

The neutral solution of aureomycin (as originally prepared) was given to rabbits under 'Nembutal' (pentobarbitone sodium) anæsthesia by intracisternal injection. 6 rabbits were each given a single injection of 0·2 ml. of the solution (0·1 mg. of aureomycin). 2 rabbits were killed after twenty-four hours, and 2 after forty-eight hours. In these 4 rabbits histological examination showed only minimal meningeal reaction. The 2 remaining rabbits were observed for a fortnight and appeared perfectly well throughout that time. None of the rabbits showed any toxic signs attributable to the aureomycin.

4 rabbits were given a similar intracisternal dose daily for seven days and killed twenty-four hours after the last injection. Necropsy showed slight browning over the pons, but microscopically the meninges showed little, if any, more inflammation than was seen in the rabbits given only a single injection. The changes observed are comparable with those reported after intrathecal injection of penicillin (Abraham et al. 1941, Cutting et al. 1945).

Therapeutic Trial

Since this preparation proved innocuous in rabbits, it was decided to use it in the treatment of 3 cases of meningitis caused by organisms resistant to penicillin and streptomycin. A single test injection was also given in 2 cases of inoperable malignant tumour of the brain without detectable adverse effects. One patient received 1 mg. and the other 2 mg. (see table II), and satisfactory aureomycin levels were maintained in the lumbar C.S.F. for four hours and seven hours. There was, however, very little aureomycin in the ventricular fluid. In case 3 (meningitis) also a preliminary test dose of 5 mg. aureomycin was given by the lumbar route, and produced a C.S.F.-aureomycin level of more than 8 µg. per ml. for twelve hours and of 1 µg. per ml. after twenty-four hours. As it was again found that the aureomycin level of the ventricular C.S.F. was low. 5 mg. was given by intraventricular injection. Five hours later there was a concentration of 4 µg. aureomycin per ml. in the ventricle and of 1 µg. per ml. in the lumbar sac. The 3 cases in which a course was given are reported below.

TABLE II—C.S.F.-AUREOMYCIN LEVELS AFTER A SINGLE INTRATHECAL INJECTION

Case	Intrathecal dose of aureomycin (mg.) and route	Source of C.S.F.	C.S.F.-aureomycin level (µg. per ml.) Hours after injection								Time for clearance from C.S.F. (hours)
			1	4	5	7	12	24	36	48	
J. G., inoperable glioma	1, L.P.	L.P.	5	5	..	..	..	0	..	..	4–24
G. D. inoperable glioma	2, L.P.	L.P.	25	4	..	2·125	..	..	..	..	..
		V.P.	0·125	..	..	0	..	..	..	..	..
Case 3, tuberculous meningitis (see text)	5, L.P.	L.P.	40	..	10	..	8	1	0·2	0	36–48
		Cist.	0·4	..	0·4	..	..	..	..	..	..
		V.P.	0·2	..	0·2	..	0	0	0	0	..
	5, V.P.	V.P.	12	..	4	..	1	0	..	..	12–24
		Cist.	12	..	3	..	..	..	..	..	..
		L.P.	0·5	..	1	..	0·2	0	..	..	12–24

L.P., lumbar puncture. V.P., ventricular puncture. Cist., cisternal puncture.

Case 2.—A youth, aged 19, had severe tuberculous meningitis with a complete spinal block. He was receiving full doses of intrathecal streptomycin and was improving steadily, being alert though confused, when he developed a secondary infection due to a micrococcus. Within forty-eight hours he was deeply comatose, with dilated pupils and stertorous breathing. By this time it was known that the infecting organism was insensitive to penicillin and streptomycin but sensitive to aureomycin 0·4 µg. per ml. It was concluded that intrathecal aureomycin afforded the only chance of recovery. He was therefore given 2·5 mg. of the preparation described above, twelve-hourly, alternately into the ventricle and the cisterna magna, and this maintained a C.S.F.-aureomycin level above 1 µg. per ml. On the fourth day the aureomycin was increased to 10 mg. twelve-hourly, and on this régime the C.S.F.-aureomycin level before each injection was 60–100 µg. per ml. For forty-eight hours he improved, and, although he did not regain consciousness, the degree of coma lightened to the point where he responded briskly to painful stimuli. He then developed bronchopneumonia and became once more deeply comatose, until, on the fourteenth day, he collapsed and died within twenty-four hours.

At necropsy, in addition to the expected tuberculous meningitis, which was severe, there was widespread cortical venous infarction. Microscopically this appeared recent and had probably occurred at the time of his final clinical collapse. There was no evidence of active purulent meningitis over the cerebral hemispheres, though over the frontal lobes there was some collagenous thickening of the leptomeninges.

This young man was treated for seven days and received a total dosage of 97 mg. of aureomycin intrathecally; and, although intracellular cocci were still seen in the films, no further positive cultures were obtained. The C.S.F.-aureomycin level fell very slowly, and at the time of death, eight days after the last intrathecal injection of aureomycin, there was still 0·8 µg. of aureomycin per ml. in the cisternal fluid. As the C.S.F. was sterile, the sensitivity of the organism could not be re-estimated.

Case 3.—A 4-year-old boy with tuberculous meningitis had been treated with streptomycin for ten months. He had never regained consciousness and had developed severe hydrocephalus, the capacity of the lateral ventricles being at least 600 ml.; his prognosis could hardly have been worse. In the final stages of his illness the child developed a secondary infection with an aerobic spore-bearing organism, akin to *B. subtilis*, which was growing freely in every specimen of C.S.F. This organism was sensitive to aureomycin 1 µg. per ml., but neither to penicillin nor to streptomycin. After the two preliminary injections of aureomycin, mentioned above, the boy was given aureomycin 5 mg. twelve-hourly alternately by the ventricular and lumbar routes. On this dose the concentration of aureomycin in the lumbar sac before each dose was 2–20 µg. per ml. and the concentration in the ventricle was 0·5–1·0 µg. per ml. These differences are at least partly attributable to dilution of aureomycin in the huge ventricles.

On this dosage the infecting organism could still be cultured from the C.S.F. Accordingly on the sixth day of treatment the dose was increased to 5 mg. of aureomycin twelve-hourly into the ventricle, with an added lumbar dose of 2·5 mg. daily. This treatment was given for twenty-four days, with two rest periods of three days each. The lumbar C.S.F. became sterile, but the ventricular C.S.F. did not, and the child's condition remained stationary. The sensitivity of the organism had not changed.

As we had so far failed to sterilise the ventricular C.S.F., and as the child's condition was deteriorating, the dose was raised, and he was given on three consecutive days two doses of 10 mg., two doses of 20 mg. and, finally, two doses of 40 mg. intraventricularly twelve-hourly. The only sign of toxicity, even on this last dose, was that the child became a little more irritable. The ventricular concentration of aureomycin twelve hours after the last dose (40 mg.) was 20 µg. per ml., and the ventricular C.S.F. became sterile for five days. The patient had then had a total of 437 mg. of aureomycin into the cerebrospinal pathways, and treatment was stopped. He died eight days later, after a total-air replacement. At necropsy the appearance was typical of tuberculous meningitis, with a basal exudate, hydrocephalus, and some mild granular ependymitis.

There was no evidence of damage caused by the large amount of aureomycin, and the ventricles were free from exudate, which was remarkable in a child who had had a purulent meningitis for a month.

Case 4.—A man, aged 48, had a *Ps. pyocyanea* meningitis following a severe head injury with a fracture through a chronically infected ear and mobile bilateral fractures of the

TABLE III—CELL AND PROTEIN CHANGES IN C.S.F. RECORDED AT SAME TIME AS C.S.F.-AUREOMYCIN LEVELS SHOWN IN TABLE II

Patient	Dose of aureomycin (mg.) and route	Source of C.S.F.	Constituents of C.S.F.	Before injection	Hours after injection						
					1	4	5	7	12	24	48
J. G.	1, L.P.	L.P.	Cells	41	44	79	..	..	..	39	..
			Protein	Over 1000 mg. per 100 ml. throughout							
G. D.	2, L.P.	L.P.	Cells	76	39	45	..	42	..	..	..
			Protein	..	90	..	..	130	..	..	..
Case 3	5, L.P.	L.P.	Cells	110	182	..	180	..	4200*	150	110
			Protein	160	..	..	120	..	140	200	170
	5, V.P.	V.P.	Cells	33	175	..	..	..	191	137	143
			Protein	75	45	..	..	..	90	100	..
		L.P.	Cells	..	424	..	390	..	480	116	110
			Protein	..	110	..	110	..	160	140	160

* See explanation in text.

maxillæ. The infecting organism was inhibited only by 50 µg. aureomycin per ml. and hence was virtually insensitive; but, as other forms of chemotherapy had demonstrably failed during the previous six weeks, and as the patient's condition was desperate, aureomycin was given as a forlorn hope. He received 10 mg. of aureomycin eight-hourly into the ventricles for three days; his temperature fell, he became less confused, the C.S.F. became sterile, and the cell-count fell. Treatment was stopped, but after another four days the organism reappeared in the C.S.F. The patient had a dural tear over his sphenoidal sinus, and the recurrence may have been related to this. A second course of intrathecal aureomycin was given; but, although the sensitivity of the organism in vitro remained the same, he did not respond again and died five days later. The ventricular C.S.F. taken immediately before each injection had an aureomycin concentration falling below 50 µg. per ml., which was the inhibitory level for this organism; in fact, it varied between 10 and 30 µg. per ml. At necropsy it was found that, as had been feared, the ventricles had become loculated.

In spite of the failure to respond to the second course of aureomycin, we were much encouraged by the unexpectedly good response to the first course, because this showed the possibility of effective treatment even when the organism was relatively insensitive to aureomycin.

Toxicity

These observations suggest that aureomycin, suitably prepared, is as little toxic to the central nervous system as to the other tissues of the body. There were no clinical manifestations of toxicity from intrathecal aureomycin, except for a trivial increase in irritability in case 3 after the very large dose of 40 mg. The amounts of cells and protein in the C.S.F. did not increase after injections of aureomycin, even when very high levels (60–100 µg. per ml.) were maintained for thirty-six hours (case 2). Table III shows the C.S.F. analyses after a single injection. The patient with meningitis naturally had a raised cell-count, and the isolated high reading of 4200 cells per c.mm. twelve hours after the injection was related to his infection. This is shown by the fact that further injections were not followed by any increase in the number of cells.

CONCLUSIONS

The systemic administration of aureomycin proved capable of setting up only low C.S.F.-aureomycin levels, regardless of whether or not active meningitis was present. When, however, a neutral preparation of aureomycin was given intrathecally, very much higher levels were established; moreover these could be increased at will by increasing the dosage.

No ill effects were detected after intrathecal injection, either in experiments on animals or in the patients under treatment, even when very high C.S.F.-aureomycin levels were maintained, as in case 2.

The therapeutic results were disappointing in th only 1 of the patients survived; but it must b remembered that all 3 patients were desperately il 2 with tuberculous meningitis and 1 with a severe hea injury, when the secondary infection supervened. The condition was deteriorating when aureomycin therap was begun, and it is clear that they survived longer tha was to have been expected had they not been treate with aureomycin. We therefore think that intratheca aureomycin is worth a further clinical trial.

SUMMARY

In 14 out of 15 patients systemic aureomycin did no produce therapeutic levels in the C.S.F.

Two side-effects have been observed following systemi aureomycin: (1) a fall in blood-pressure in hypertensiv patients; and (2) a fall of C.S.F. pressure in both norma and hypertensive patients.

A method of preparation of aureomycin for intra thecal use is described. This preparation was given t 3 patients with meningitis, and a concomitant improve ment in their condition was seen, although recover was not achieved.

Using this preparation it has been possible to achieve C.S.F.-aureomycin levels unobtainable by any other method and without causing any untoward reaction.

Intraventricular or cisternal injection is probably essential to obtain satisfactory C.S.F.-aureomycin levels.

We are grateful to Prof. Sir Hugh Cairns, Dr. Honor Smith, and Dr. R. L. Vollum for their encouragement and advice We are particularly indebted to Mr. G. Higgins, B.SC., of the department of biochemistry, without whose expert aid and advice the preparation could not have been made; and to Mr. R. N. Arnatt for his indispensable help in doing the large number of time-consuming estimations required. We should also like to thank the members of the pharmaceutica department and the nurses of the United Oxford Hospitals for their most willing coöperation. The aureomycin was supplied by the Medical Research Council and by Messrs. Lederle.

REFERENCES

Abraham, E. P., Chain, E., Fletcher, C. M., Gardner, A. D., Heatley, N. G., Jennings, M. A., Florey, H. W. (1941) *Lancet*, ii, 177.
Cairns, H., Davidson, M. A. (1951) *Ibid*, ii, 411.
Cutting, W. C., Halpern, R. M., Armstrong, C. A. (1945) *Proc. Soc. exp. Biol., N.Y.* 58, 183.
Dowling, H. F., Lepper, M. H., Caldwell, E. R. jun., Whelton, R. L., Brickhouse, R. L. (1949) *J. clin. Invest.* 28, 983.
Drake, M. E., Bradley, J. E., Imburg, J., McCrumb, F. R. jun., Woodward, T. E. (1950) *J. Amer. med. Ass.* 142, 463.
Harvey, J. C., Mirick, G. S., Schaub, I. G. (1949) *J. clin. Invest.* 28, 987.
Schoenbach, E. (1949) *Med. Ann. District of Columbia*, 18, 290.

PARA-ACETAMIDOBENZALDEHYDE THIOSEMICARBAZONE* IN THE TREATMENT OF LEPROSY

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THE antituberculous action of the thiosemicarbazones was first studied in Germany and was reviewed in 1950 by Domagk and by Mertens and Bunge. *p*-Acetamidobenzaldehyde thiosemicarbazone ('T.B.I') was the one which appeared most promising.

Any remedy of value in tuberculosis is likely to be of value in leprosy also. Trials here were delayed by warnings about toxicity received from workers in the United States. In August, 1950, however, Ryrie gave an account of a trial in leprosy, and though his report dealt with only 10 cases treated for only four months, the results were encouraging. Also Vegas et al. (1950) reported on the treatment of 42 cases of leprosy for from three to six months with a good response. Schneider et. al. (1950) described the use of T.B.1 in 14 patients for periods up to eleven months, with good clinical response but no consistent reduction in the number of bacilli in the lesions. They regarded T.B.1 as equal to sulphones, if not superior to them.

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* This substance (T.B. 1/698) is marketed under various names: 'Conteben,' 'T.B.I,' 'Tibione,' 'Berculon A,' thiacetazone, &c.

A trial was begun here in September, 1950; and the number of patients under treatment steadily increased till in October, 1951, about 100 patients were being treated with *p*-acetamidobenzaldehyde thiosemicarbazone supplied by Imperial Chemical (Pharmaceuticals) under the name 'Berculon A.'

The present report deals with 71 patients treated for five months or more; the longest period of treatment is thirteen months, and the average eight and a half months.

The cases treated fall into three groups:

	No. of cases
Group A: cases of lepromatous type, previously untreated	30
Group B: cases of tuberculoid type, previously untreated	28
Group C: cases of lepromatous type, previously treated with sulphone, but with difficulty because of complications	13
Total	71

METHOD

Berculon A was administered in tablets of 50 mg. as follows:

First three or four days	.. 1 tablet a day
Second " " " "	.. 2 tablets a day—1 in the morning and 1 in the evening
Thereafter	.. 3 tablets a day—1 in the morning and 2 in the evening

SPECIFIC TOXIC EFFECTS

Many reports of the toxic effects of T.B.1 have been published. The early German work was done with doses much higher than those now used, and toxic effects were more common and serious than now. Even with the lower doses now used, some workers, particularly in the United States, regard the drug as too toxic for the treatment of tuberculosis; but that is not the opinion of the majority.

The effects recorded include anorexia, headache, epigastric discomfort, vomiting, and other evidence of disturbed liver function; fever and rashes; a mild hæmolytic anæmia; and agranulocytosis (rarely). Thus there is evidence of damage to the liver and to the bone-marrow.

In the present 71 cases, serious toxic effects were seen in only 1 patient, who had acute agranulocytosis.

A young man, in good physical condition, with tuberculoid leprosy, was treated with T.B.1 50 mg. a day for the first week, 100 mg. a day for the second week, and 150 mg. a day for the third and fourth weeks. He then appeared one morning complaining of malaise and pain in the teeth. That afternoon his temperature was 103°F. He was ill and toxic and his tooth sockets, tonsils, fauces, and the nail beds of the toes were acutely inflamed. An acute agranulocytosis was diagnosed and confirmed by blood examination, and intensive penicillin treatment was instituted, 1,000,000 units of procaine penicillin in oil being given each day. The clinical condition subsided in three days, except that small necrotic areas on the toes took several weeks to heal. The white-cell counts before treatment started and during and after this incident are shown in the accompanying table.

The striking features were a decrease of more than 90% in the total granulocytes; a decrease of 82% in the polymorphs, with a return to the previous figure in a week; and the almost complete disappearance of eosinophils, which had previously been very numerous (associated with filariasis due to *Acanthocheilonema perstans*), and their failure to reappear until the third week.

The clinical picture and the blood picture were those of an acute toxic agranulocytosis, which was fortunately diagnosed and treated early. The toxic effect of T.B.1 on the bone-marrow and on the production of granulocytes has been recorded by others. No such case has been seen here before, although several hundred patients have been treated with sulphone for several years, and routine blood-counts are made before treatment and repeated whenever any illness develops during treatment. There seems little doubt that the condition was caused by the T.B.1.

WHITE-CELL COUNTS IN AGRANULOCYTOSIS DUE TO T.B.1

Stage	Total	Granulocytes: Polymorphs	Granulocytes: Eosinophils	Granulocytes: Total	Lymphocytes	Monocytes	Basophils
Before treatment	10,300	2781	3090	5871	3914	515	Nil
Day of illness: 1	3800	422	54	476	2682	266	76
2	3500	455	nil	455	2730	315	Nil
3	3000	570	nil	570	2250	180	Nil
3	3100	496	62	558	2325	217	Nil
4	3700	777	nil	777	2553	370	Nil
6	4200	1890	nil	1890	2096	294	Nil
7	4500	1890	45	1935	2295	270	Nil
8	6000	2640	nil	2640	3180	180	Nil
9	6500	2860	nil	2860	3445	195	Nil
10	6000	2160	60	2220	3600	180	Nil
11	6200	2976	nil	2976	2976	248	Nil
13	6200	2604	nil	2604	3472	124	Nil

In this case T.B.1 treatment was abandoned, and treatment with sulphone was given, with no further complications.

In the other 70 out of the 71 cases only minor toxic effects were seen. Anorexia and epigastric discomfort were recorded in 12 cases; treatment was maintained, in some cases at a lower dose for a few days, and the symptoms subsided. Fever and rash developed in 2 cases; in one of these the cessation of treatment was rapidly followed by the disappearance of the fever and rash, and treatment was soon resumed with no trouble; in the other the fever and rash continued much longer, but the patient was never seriously ill, and treatment has now been resumed.

In the early phases of the work, routine tests for toxicity were used, particularly after the case of agranulocytosis occurred; but later the routine tests were abandoned.

Thus we find that T.B.1 is usually well tolerated in leprosy, and that toxic effects are much less common than has been reported in tuberculosis. This experience agrees with that of Vegas et al. (1950), who gave in leprosy more than 300 mg. a day and in some cases 900 mg. a day. They expressed the view that the toxic effects of T.B.1 seen in tuberculosis were produced by the liberation of bacillary toxins in persons sensitive to them, and that in leprosy this factor did not operate because in lepromatous cases there was anergy to the products of the bacilli. This idea needs more evidence to support it, but it is in accord with our knowledge of leprosy in general.

COMPLICATIONS OF TREATMENT

Under the heading of complications we consider those conditions which, though caused by leprosy and often seen entirely apart from chemotherapy, may be precipitated and made more common, and perhaps more severe, by chemotherapy.

They include acute and subacute "reaction" with fever, swelling of lesions, and "*erythema nodosum*," and also the severe neuritis and the inflammations of the eye, which may appear as part of the general "reaction," or may be seen separately, apparently as a purely local manifestation of reaction.

These conditions are confined to the lepromatous cases, and they are therefore discussed under the results of treatment in groups A and C.

RESULTS

Group A

This group consists of 30 lepromatous cases, many of them severe, all having had *no previous* chemotherapy of any kind. The duration of the T.B.I treatment in this group varies between five months and thirteen months, and averages nine months.

Complications of Treatment.—In only 7 of the 30 cases have any complications occurred. "Reaction" has been recorded eight times, neuritis once, and iritis once. In 5 patients there has been only one such incident recorded; the other 2 patients showed two such incidents. Of the "reactions," three were recorded as severe and the remaining five as mild. Both the iritis and the neuritis were recorded as mild. All these incidents have been of short duration.† Thus the incidence and severity of the complications of treatment were low, probably lower than would be expected in a similar group of cases treated with sulphone.

Clinical Response to Treatment.—In all of the 30 cases clinical improvement has been seen. The skin lesions have become less prominent, and the general condition has improved. In some cases, especially in those treated for a longer period, the clinical improvement has been considerable; in the group as a whole the improvement has been satisfactory.

Bacteriological Improvement.—In 21 out of the 30 cases definite bacteriological improvement has been seen (a definite decrease in the number of bacilli found in "smears" made from the lesions by standard methods). 2 cases (both mild lepromatous cases graded only 1 plus) have become negative. This bacteriological improvement in the group as a whole is considered satisfactory.

Group B

This group consists of 28 cases of tuberculoid type, all of them active, and most of them highly active, treated with T.B.I for periods varying between six months and thirteen months, and averaging nine months. No complications have been seen in these cases.

Clinical Response to Treatment.—In all these cases the clinical activity of the lesions in the skin has slowly subsided, the subsidence usually being complete within six months, the patches becoming flat and "residual." The thickening and tenderness of nerves have subsided, but more slowly. Thus the clinical response in these cases has been satisfactory.

Bacteriological Improvement.—As is usual in such cases, nearly all of them were bacteriologically negative before treatment started, and remained so during treatment. One case was bacteriologically positive but rapidly became negative.

Group C

This group consists of 13 cases, all lepromatous cases, in which previous sulphone tratement had been given for considerable periods, but in which the frequency or severity of complications (reaction, neuritis, &c.) had rendered sulphone treatment difficult. They were *selected out of nearly 400 patients* on routine sulphone treatment. This group was therefore, by its nature, bound to present difficulties in treatment. The period of the treatment varies between five months and thirteen months, and averages nine months.

Complications of treatment in these cases have been numerous, such incidents recorded numbering 36, but in almost every case these complications have been less frequen and less severe than during the previous sulphone treatment Moreover, as the treatment continues, these complication become fewer. In all the 13 cases the treatment has bee maintained, but short breaks have been numerous, and a few longer breaks have been thought advisable.

Clinical response to treatment has been definite in 12 out of these 13 cases.

Bacteriological improvement has been recorded in only 5 of the 13 cases. This number is low, probably because the previous sulphone treatment had reduced the number of bacilli, and the later phases of bacteriological improvement under treatment are always slow.

DISCUSSION AND CONCLUSIONS

The warnings received about the toxicity of T.B.I have, on the whole, not been justified by the experience described above; it seems possible if not probable that, as Vegas et al. (1950) suggest, patients with leprosy tolerate T.B.I much better than patients with tuberculosis. The one alarming feature was the occurrence of the case of acute agranulocytosis. Apart from this incident, which was not repeated in the following eight months, the treatment was well tolerated; but more experience is needed before final conclusions regarding its safety can be reached.

The data here given do not justify any attempt at a definite assessment of the value of T.B.I in leprosy. They do, however, give certain indications, and some comparison with other forms of treatment are justified:

(1) T.B.I has one big advantage over sulphone, in that there is very little evidence that patients become allergic to it. With sulphone, in West Africans in particular, this has been the main difficulty.

(2) Apart from this, in the non-lepromatous cases which here in Nigeria and in some other countries form the large majority, T.B.I has no obvious advantage over sulphone treatment. Both are well tolerated and produce similar results. Sulphone treatment with twice weekly oral diaminodiphenylsulphone (D.A.D.P.S.) is much simpler and cheaper.

(3) In lepromatous cases, particularly in the more severe ones, T.B.I has certain definite advantages in addition to the rarity of allergy: the complications of treatment are fewer and less severe, and the maintenance of treatment without breaks is more often possible.

(4) The early results (up to thirteen months' treatment) appear to be as good as with sulphone. The late results cannot yet be assessed. There is as yet no clear indication that T.B.I is more effective and quicker in its action than sulphone, or that it will reduce the period of treatment necessary to render the disease inactive and the lesions bacteriologically negative; but this possibility cannot be ruled out.

(5) So far it seems that T.B.I must be given at least once a day several days a week, whereas sulphone treatment is best given twice weekly, and can be given once weekly. Thus, sulphone treatment is much more widely applicable in countries such as Nigeria. Moreover sulphone treatment is much cheaper.

(6) In countries such as Nigeria sulphone treatment with D.A.D.P.S. given orally seems likely to remain the basic treatment for leprosy. In other countries, where conditions are different, with fewer patients mostly in leprosy institutions under close medical supervision, T.B.I may be found preferable.

(7) In Nigeria and in other countries with similar conditions T.B.I should prove a very useful alternative treatment to sulphones in certain types of case—e.g., in patients who become allergic to sulphones, and in lepromatous cases in which complications are common or severe (in this second type of case, the treatment needs close medical supervision, and admission to a leprosy institution is recommended).

(8) At present, at any rate, T.B.I treatment should be confined to patients resident in leprosy institutions with adequate medical staff. Patients needing the treatment should be transferred to such institutions.

(9) If further cases of agranulocytosis occur, it may be advisable to abandon this form of treatment.

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† Since this report was written, one severe and protracted case of iritis has recently been seen in this group.

SUMMARY

p-Acetamidobenzaldehyde thiosemicarbazone (T.B.1) has been used in the treatment of leprosy since September 1950.

Experience in 71 patients treated between five months and thirteen months is described. Apart from 1 case of acute agranulocytosis, no serious toxic effects were seen. The treatment was well tolerated, and complications of treatment were few and usually not severe. Clinical and bacteriological response was satisfactory.

T.B.1 treatment is compared with sulphone (D.A.D.P.S.) treatment. The results of the two treatments appear similar. Allergy, shown by drug fever and dermatitis, has been rarer and much milder with T.B.1: complications of treatment ("reaction," eye inflammation, neuritis, &c.) have been fewer and milder than with D.A.D.P.S.

If agranulocytosis is found to be rare, T.B.1 should be a valuable alternative treatment to sulphone. It is much less simple to give, however, and is more expensive. At present its use should be confined to selected inpatients of leprosy institutions, patients in whom the maintenance of sulphone treatment presents difficulties. It seems to be much less widely practicable than sulphone treatment, though it has certain definite advantages.

The work here recorded was carried out by the research unit of the Nigeria Leprosy Service; thanks are due to the Director of Medical Services (Dr. S. L. A. Manuwa) and to the Assistant Director Leprosy Control (Dr. R. H. Bland) for permission to publish.

ADDENDUM

Since this article was written the period of treatment has been extended to seventeen months, and the number of patients is now 126. No further case of agranulocytosis has been seen, and no modification of the views expressed above seems necessary. Earlier references to the use of T.B.1 in leprosy, with good results, have been traced but not seen in the original. Hohenner (*Med. Klin.* 1949, p. 1378), Grosch and Kaliebe (*Zbl. Haut- u. GeschlKr.* 1950, p. 1), and Walter (*Z. Hals- Nas.- u. Ohrenheilk.* 1950, p. 218) each describe 1 case, the last two reports dealing with the same case.

I have treated 4 cases of pulmonary tuberculosis with T.B.1 continuously for the past five months; no serious toxic effects have been seen.

REFERENCES

Domagk, G. (1950) *Amer. Rev. Tuberc.* 61, 8.
Mertens, A., Bunge, R. (1950) *Ibid*, p. 20.
Ryrie, G. A. (1950) *Lancet*, ii, 286.
Schneider, J., Laviron, P., Lauret, L., Basset, A. (1950) *Bull. Soc. Path. exot.* 43, 733.
Vegas, M., Convit, J., Medina, J. A., de Blomenfield, E. (1950) *Int. J. Leprosy*, 18, 451.

THE IDENTIFICATION OF 3:5:3′-L-TRIIODOTHYRONINE IN HUMAN PLASMA

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IN a preliminary communication (Gross and Pitt-Rivers 1951), the presence of two iodine-containing compounds other than thyroxine and iodide was reported in human plasma. 3:5:3′-L-triiodothyronine has now been synthesised, and it has been shown that the compound previously named "unknown 1" behaves both on paper chromatograms and on chromatographic columns in exactly the same way as this amino-acid.

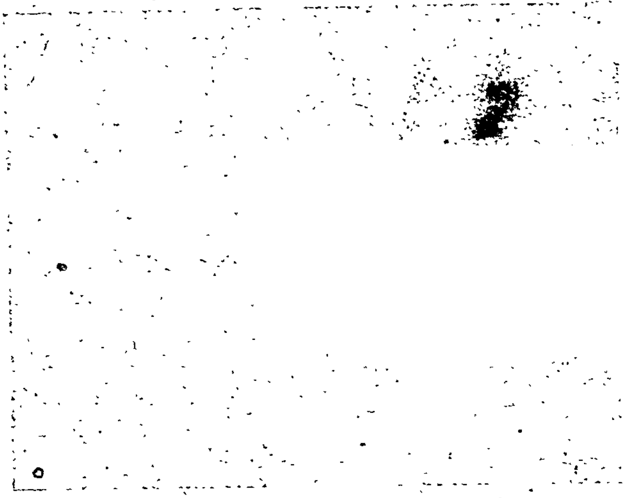

Fig. 1—Two-dimensional paper chromatogram of the plasma extract from case 2 to which 100 μg. triiodothyronine and 50 μg. thyroxine had been added. The origin is shown by the circle in the lower left-hand corner; development was with n-butanol-acetic acid in the vertical direction and with butanol-dioxan-ammonia in the horizontal direction. The thyroxine (TX) and triiodothyronine (TRI) spots corresponded exactly with the positions of radioactive thyroxine and radioactive unknown 1 (see Gross and Pitt-Rivers 1951) as shown on the corresponding autoradiogram.

METHODS

Samples of plasma were obtained from the series of patients shown in the accompanying table at various time-intervals after the administration of the radioactive iodine. The plasmas were acidified, and extracted with butanol, and the butanol extracts were evaporated as described previously. It should be noted that in the course of evaporation most of the *iodide* present in the sample is lost (fig. 2*d*).

The samples from patients 1 and 2 were placed on paper, together with 100 μg. of synthetic triiodothyronine and thyroxine, and developed two-dimensionally with two solvent pairs—butanol-dioxan-ammonia against butanol-acetic acid (fig. 1), and butanol-dioxan-ammonia against collidine-ammonia. The latter solvent was prepared according to Taurog et al. (1950), and by itself did not separate triiodothyronine from thyroxine.

The remaining extracts were analysed on a modified form of the kieselguhr column suggested by Grönkvist and Hellberg (1951).

The column was prepared from 5 g. of acid-washed kieselguhr to which has been added 4 ml. of 0·5N NaOH; this was suspended in butanol containing 20% of chloroform and packed into a glass tube with an internal diameter of 13 mm.; 3 mg. of triiodothyronine (together with 3 mg. of thyroxine in some cases) was added to the plasma extract which was then placed on top of the column and chromatographed with the butanol-chloroform solution. The effluent was passed through a liquid-flow Geiger counter at the rate of 1 ml. per 5 minutes and then fractionated in 1·5 or 3·0 ml. lots by an automatic fraction collector. The radioactivity was measured by a count-rate meter and recorded on the paper chart of a recording milliammeter. The individual fractions were recorded on the same chart by a separate pen

THE PATIENTS AND THE DOSES OF RADIO-IODINE

Patient	Dose of radio-iodine	Diagnosis
1	5 mc.	Hyperthyroidism
2	1 mc.	,,
3	4 mc.	,,
4	5 mc.	Thyroid carcinoma; euthyroid
5	100 μc.	Hyperthyroidism
6	100 mc.	Carcinoma of the thyroid functioning metastases, hypothyroid

connected to contacts in the fraction collector. The added triiodothyronine or thyroxine were measured in the fractions by the photometric estimation of the colour formed when they were treated with nitrous acid and then with alkali; the distribution of these substances in the effluent was then compared with the distribution of the radioactivity (figs. 2*a* and *b*).

Complete details of this procedure will be published later.

Because of the low radioactivity of the sample from patient 5, four successive fractions were pooled, evaporated to dryness on shallow metal plates and counted under a thin end-window counter. After counting, the material on the plates was washed off with aqueous alcohol and estimated for triiodothyronine.

RESULTS AND DISCUSSION

The relative locations of thyroxine and triiodothyronine on the paper chromatograms are shown in fig. 1. The triiodothyronine spot corresponds exactly with the location of the radioactive spot previously labelled unknown 1.

The third peak of radioactivity occurring in the eluate from the column (fig. 2*a*) corresponds with the location of synthetic triiodothyronine; this close correspondence is shown in fig. 2*b* and was found in all the samples examined. The second peak in fig. 2*a* corresponds with thyroxine.

The possibility that triiodothyronine might be an artefact of the extraction procedure was eliminated by adding tracer amounts of synthetic radioactive thyroxine to plasma and analysing the mixture on the column; fig. 2*c* shows that no triiodothyronine is formed under these conditions. Gordon et al. (1952) have shown that radioactive thyroxine added *in vitro* to plasma is indistinguishable electrophoretically from the naturally occurring thyroxine plasma-protein complex.

That triiodothyronine may be a radiation artefact is unlikely for two reasons: (1) it was detectable in the plasma of patient 5 who had received only 100 µc. of radio-iodine; and (2) it has been isolated from the thyroid tissue of animals which had not received any radioactive iodine at all (unpublished).

The radio-iodine which appears in the first peak (fig. 2*a*) is largely an artefact of the procedure. This is demonstrated in fig. 2*d* which shows the curve obtained when radioactive iodide is added to normal plasma and processed in the usual manner. At the same time thyroxine may, by destruction, contribute to this first peak (see fig. 2*c*); the nature of the compounds it contains is being investigated further.

SUMMARY

An iodine-containing substance present in the plasma of patients given radioactive iodine has been shown to behave in a manner identical with that of 3:5:3'-L-

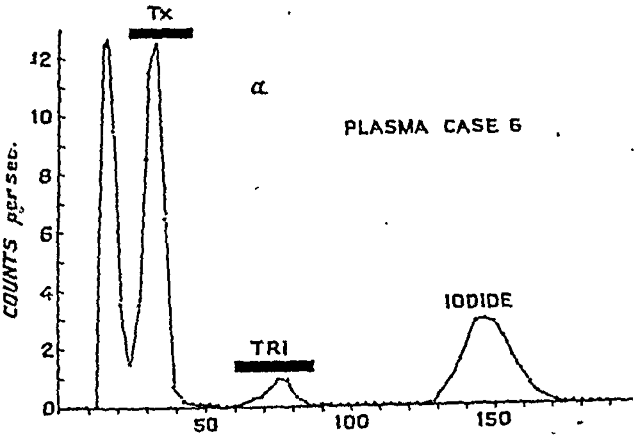

Fig. 2*a*—Analysis on a kieselguhr column of the radioactivity in a butanol extract of plasma from case 6 (24 hours after administration of radio-iodine), together with 3 mg. each of thyroxine and triiodothyronine. The curves represent the distribution of radioactivity in successive fractions of eluate from the column. The horizontal black bars indicate the positions of the added thyroxine (TX) and triiodothyronine (TRI) determined colorimetrically; the nature of the iodine in the first peak (13-20 ml. of eluate) is unknown (see fig. 2*d*).

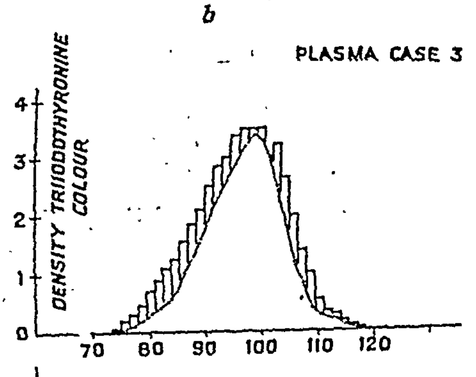

Fig. 2*b*—The triiodothyronine peak from the column analysis of the plasma extract with 3 mg. of triiodothyronine added, from case 3, 24 hours after the dose of radio-iodine. The dots indicate the concentration of radioactivity and the column. represent the concentrations of triiodothyronine in the corresponding fractions of eluate as indicated by the density of the colour reaction.

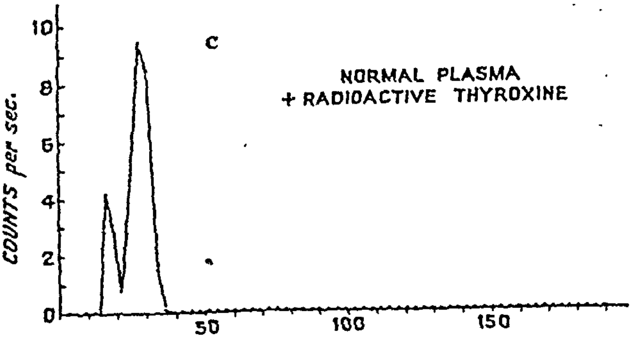

Fig. 2*c*—Column analysis of the extract from 10 ml. of normal plasma to which 0·30 µg. of radioactive thyroxine had been added before extraction. Note that no radioactivity is detectable at the usual site of the triiodothyronine peak (60-120 ml. of eluate) although some radioactivity occurs in the first peak.

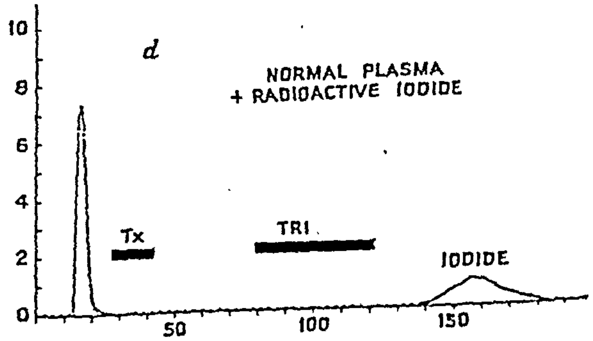

Fig. 2*d*—Column analysis of the extract from 3 ml. of normal plasma to which 5 µc. of tracer Na I^{131} had been added before extraction, plus 2 mg. each of thyroxine (TX) and triiodothyronine (TRI). Only about 1% of the added radioactivity has remained in the extract after evaporation to dryness; of this, 45% appears as iodide and 55% in the first peak. This indicates that most of the radioactivity in the first peak in fig. 2*a* is an artefact derived from iodide.

triiodothyronine on two-dimensional paper chromatograms and on a kieselguhr column.*

Evidence has been given that this compound is not an artefact of the analytical procedure or of the destructive effects of radiation.

It is concluded that 3:5:3′-L-triiodothyronine is a normal constituent of the organic iodine fraction of the plasma, since it has been found in the plasmas of both euthyroid and hyperthyroid individuals.

We are indebted to Dr. A. J. P. Martin for much help throughout this work. We also wish to thank Dr. E. E. Pochin and Dr. N. B. Myant for providing the plasma samples, Mr. P. Bovill for help with the analytical procedure, and Mr. C. Sutton and Mr. E. Hitchcock for the autoradiograms and photographs.

REFERENCES

Gordon, A. H., Gross, J., O'Connor, D., Pitt-Rivers, R. (1952) *Nature, Lond.* 169, 19.
Grönkvist, K. E., Hellberg, H. (1951) *Farma. Revy,* 50, 189.
Gross, J., Pitt-Rivers, R. (1951) *Lancet,* ii, 766.
Taurog, A., Tong, W., Chaikoff, I. L. (1950) *J. biol. Chem.* 184, 83.

MERCURY AND PINK DISEASE

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AN association between mercury and pink disease (infantile acrodynia) was suggested by the work of Warkany and Hubbard (1948, 1951), Fanconi et al. (1947), and Fanconi and Botsztejn (1948). In 38 of 41 investigated cases Warkany and Hubbard found an abnormal quantity of mercury excreted in the urine. Other workers (Bivings and Lewis 1948, Elmore 1948, van Crefeld and Paulssen 1949, Lefebvre 1949, Loebenstein 1949, Watkins 1950, Kromann 1950) have supported Warkany's and Fanconi's claims.

In Manchester pink disease is relatively common. In the three Manchester children's hospitals during 1950 the numbers of cases given this diagnosis were:

Royal Manchester Children's Hospital	37
Booth Hall Hospital	7
Duchess of York Hospital for Babies	17
Total	61

These figures probably give a reliable picture of the incidence of pink disease, because it is fair to assume that most of the affected infants come to hospital at some stage of their illness.

The use of powders to prevent or to cure teething difficulties is widespread. Such powders are variously labelled as "teething" or "cooling" powders, and some of them contain mercury in relatively large quantities. Their content of calomel varies from 16 to 33%.

INVESTIGATION AND RESULTS

We have approached the problem of mercury in pink disease from various angles.

(1) We followed up many cases in the hope of finding some other form of clinical hypersensitivity to mercury or an association with other allergic disorders in the patients or their families.

(2) We tried to find the incidence of the ingestion of mercurial teething powders among a healthy infant population and its regional and numerical correlation with pink disease.

(3) The urinary excretion of mercury was studied.

(4) The response to dimercaprol (BAL) was investigated.

Follow-up

The children followed up were those in whom pink disease had been diagnosed at the Duchess of York Hospital for Babies in 1930–50. The case-notes of 213 patients were available. Of these 37 had died, the cause of death, so far as could be ascertained, being as follows:

Mortality in 213 cases

Pink disease	16
Bronchopneumonia	12
Sudden death	4
Empyema + fibrinous pericarditis	1
Gastro-enteritis	1
Bronchiectasis	1
Bronchiolitis	1
Septicæmia	1
Total	37 *(17%)*

The main single complication leading to a fatal outcome was bronchopneumonia. In 4 cases death took place suddenly. In 16 cases no definite cause of death was found and death was *attributed* to the primary illness.

Of the remaining 176 patients 110 were re-examined, and a detailed history was obtained from the parents, particularly with regard to exposure to mercury, sequelæ of the disease, and allergic disorders. In 80 (73%) development had been normal, mentally and physically; the other 30 (27%) were described as nervous or highly strung, some of them having temper tantrums, nocturnal enuresis, *nail-biting*, exaggerated fears, and stammer. One girl still keeps rubbing her hands, and the mother maintains that this dates back to her acrodynia.

In only 10 patients could a history of allergic disorders be elicited. In most of them these were urticarial rashes, and only 1 had asthma. In 7 other cases a family history of allergy was obtained. Thus 15% of the patients had some relationship to the allergic diathesis. This figure comes well within the suggested range of allergic disorders among the general population.

No instance of recrudescence or second illness was reported.

5 children with severe pink disease showed simultaneous recovery from an intercurrent infection and the acrodynia. The intervening illnesses were measles in 3 cases, chickenpox, and tonsillitis.

Mercurial Teething Powders

In 97 cases a clear answer was given to the question of exposure to mercury: 49 children (50%) had received mercurial teething powders. In 29 cases these had been given before the onset of their illness, while in the other 20 they had been given to alleviate its manifestations. Thus almost 30% had certainly ingested mercury, often for many months, before the beginning of the pink disease. In 5 cases the child had had mercurial teething powders throughout the illness and for years afterwards without ill effect.

A relatively high incidence of ingestion of mercury by affected infants having been found, it seemed of desirable import to ascertain how frequently teething powders are given to the healthy infant population. The subjects of this inquiry were 1561 infants, from four months to two years of age, attending the welfare centres of Manchester and Salford public-health authorities. Of these, 619 (39·6%) had received teething or cooling powders of various kinds, and in 109 (6·9%) these were mercurial.

As the habit of giving babies teething powders may vary considerably from region to region, we then chose another area where we knew that the incidence of pink disease was low—i.e., the county of Warwick, where there are 5–10 cases a year in a population about half that of Manchester and Salford. The parents of 1588

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* We have recently been informed by Dr. William E. White from the Veterans Administration Hospital, San Francisco, that he too has detected, on paper chromatograms of human plasma, an unknown iodinated compound, which he suspects to be triiodothyronine.

Warwickshire children of the same age-group were questioned and it was found that 679 children were habitually given teething powders, which in 584 cases (37%) contained mercury.

In the Manchester and Salford areas the incidence of pink disease did not seem to be higher in the districts where mercurial teething powders were commonly given to infants.

Urinary Excretion of Mercury

The urine of children who had had active pink disease during the past two and a half years was examined for mercury. The analysis was made by two different laboratories using the same method but varying in the form of collection, one using heavy metal-free glass containers, the other ordinary glass bottles. Each laboratory established a normal range of mercury excretion, which was slightly higher in that using ordinary bottles. Of 94 cases examined no abnormal excretion of mercury was detected in 33 (35%), and 61 (65%) had increased amounts, ranging from 20 to 250 µg. per 100 ml. The 65% with an abnormally large quantity of mercury in the urine compares well with the 50% in the follow-up group who had been given mercury either before or after the onset of pink disease.

Patch Tests

Patch tests with calomel, calomel ointment, and blue ointment were made on 10 patients with florid acrodynia, and a positive result was obtained in 1. This child, whose skin reacted strongly to blue ointment, showed a weaker response to calomel powder. Among 30 healthy infants and children 1, who had never (so far as could be ascertained) ingested mercury previously, gave a mild reaction to calomel.

Response to Dimercaprol

Dimercaprol was given to 15 infants who were said to have ingested mercury for many months before the onset of pink disease and in whom a high urinary excretion of mercury was found. The treatment was given in hospital, and the patients were carefully observed. The dose used was 1 mg. per lb. of body-weight according to the schedule suggested by Bivings and Lewis (1948). Maximal excretion of mercury in the urine was noticed within twenty-four hours of the start of treatment and gradually decreased in the course of treatment.

In all the cases there was a definite change in emotional behaviour. The patients became less irritable, smiled again, and took their feeds more readily; 4 gained weight during treatment; 3 lost their skin rash; and in 2 the perspiration decreased. All the other clinical manifestations, such as pinkness of hands and feet, hypotonia, tachycardia, pain in the extremities, and (in the majority) perspiration, persisted.

In 3 infants, however, who did not present the characteristic clinical picture of acrodynia but only certain manifestations which are commonly associated with it, dimercaprol produced definite improvement, and laboratory findings supported the opinion that this was due to the elimination of mercury in the urine. An account of these is given because they are regarded as evidence that chronic ingestion of mercury produces changes in the serum-cholesterol, probably due to renal damage, simultaneously with symptoms like those of acrodynia. They thus establish a link between the accepted forms of mercury poisoning and acrodynia.

CASE-RECORDS

Case 1.—*A boy, aged 21 months, was brought to the out-patients' department because of a change in his behaviour. For the past month he had become fretful, crying frequently, refusing to play with his toys, disinclined to walk, and preferring to lie on the floor. He had little appetite. He had been given a mercurial teething powder from the age of 4 months, three to four times weekly, for nearly a year, until six months ago, when the dosage was gradually reduced, and during the past four weeks he had had only one powder. On examination he appeared well nourished but rather pale;* and there was no pinkness of hands or feet, but only slight hypotonia and a pulse-rate of 120. A non-pitting œdem over the dorsum of both feet and a chronic nasal infectio were the most noticeable findings. He had much albuminuri and because of this was admitted to hospital.

The concentration of albumin in the urine was 1%. A one-way chromatogram in phenol revealed bands similar t those seen in nephrosis. The amount of mercury in the urin was 102 µg. per 100 ml. Examination of the blood showed:

Serum-cholesterol	585 mg. per 100 ml.
Serum-chlorides	685 mg. " " "
Serum-proteins	6·61 g. " " "
Albumin	2·6 g. " " "
Globulin..	4·01 g. " " "

Because of the heavy mercury ingestion and excretion dimercaprol was given for eight days. The albuminuri decreased daily and ceased entirely a fortnight after the en of treatment. The child's behaviour improved, and serum cholesterol and serum-protein levels reverted to normal.

Case 2.—*A girl, aged 7 months, was brought to hospita with intractable conjunctivitis. She had had diarrhœa and vomiting for five days preceding the eye trouble, and consequently had lost weight. For the past two months she had had a mercurial teething powder nightly.*

On examination severe photophobia was the only pathological finding. Nothing was found on routine laboratory examination of the urine, and the amount of mercury in the urine was 150 µg. per 100 ml.

The teething powder was discontinued, and after ten days the urinary excretion of mercury had decreased to 32 µg. per 100 ml. The photophobia had somewhat improved but was still disturbing. The serum-cholesterol was 396 mg. per 100 ml.; the serum-protein was normal. After treatment with dimercaprol the photophobia cleared completely, and the serum-cholesterol returned to normal.

Case 3.—*A boy, aged 15 months, was admitted to hospital with typical acrodynia. He had had mercurial teething powders twice weekly for the past nine months, the last one a few days before his arrival in hospital. His urine contained mercury 52 µg. per 100 ml. The serum-cholesterol was 525 mg. per 100 ml.; the serum-protein was normal. After treatment with dimercaprol the urinary excretion of mercury ceased, the serum-cholesterol was 230 mg. per 100 ml., the infant began to gain weight and was more cheerful, but all the other manifestations persisted for many weeks.*

The results of treatment with dimercaprol in cases 1–3 may be summarised as follows:

Case no.	Before treatment		After treatment	
	Serum-cholesterol (mg. per 100 ml.)	Mercury in urine (µg. per 100 ml.)	Serum-cholesterol (mg. per 100 ml.)	Mercury in urine (µg. in 100 ml.)
1	585	102	202	0
2	396	150	190	18
3	525	52	230	21

DISCUSSION

Warkany and Hubbard (1951) have marshalled weighty evidence that mercury can cause pink disease. Particularly, the finding of an abnormal amount of mercury in the urine in some 93% of their cases is of great importance. However, the criticism may be made that the cases examined may have been subjected to unintentional selection, because they were referred to Warkany and Hubbard by pædiatricians of other cities especially for the estimation of urinary mercury. In our series about 72% of patients had mercury in their urine, and as *only* 6·9% of the local child population were in the habit of taking mercurial teething powders this finding *strongly points* to this metal as an important ætiological factor in pink disease. But there may well be other factors which, either in *conjunction* with mercury or independently, can produce the clinical picture of acrodynia. This is suggested by the fact that in Warwickshire, where 37% of the children were found to have had mercury teething-powders, the incidence of acrodynia is much lower.

A further point deserving consideration is the age-distribution. Most of the cases in this as well as in other series published in this country (Fisher 1947) occur in the first and second years of life. In Switzerland (Fanconi et al. 1947) and in France (Cosmi 1930) most cases occur in the second, third, and fourth years of life. This could be related to different habits of using mercury indiscriminately. In this country mercurial teething or cooling powders are given to infants, while in France and Switzerland santonin and calomel are given to older children as anthelmintics. The allergic response to the ingestion of mercury known as calomel disease (Jenny 1930, Fanconi et al. 1947, Baumann 1949), is hardly ever seen in infants aged less than 1 year old.

The seasonal incidence in our series favours the months of spring. In view of the insidious onset of pink disease, this might be due to the higher incidence of upper respiratory infections during the winter months and with it a large number of fretful and irritable infants providing their parents with an opportunity to treat supposed teething troubles with teething powders.

If mercury is an ætiological factor, a further question arises: is it to be regarded as a poison or a sensitising agent ?

Fanconi and his co-workers support their concept of pink disease as a neuro-allergic manifestation with the observations that it has followed single administrations of santonin and calomel; that the age-distribution is similar to that of calomel disease, which undoubtedly can be regarded as an antigen-antibody response; and that Landolt and Egli (1948), in Switzerland, found allergic disorders in 32% of former acrodynia patients. The Swiss workers also include polyradiculitis and lipoid nephrosis among the hypersensitivity reactions to mercury.

Warkany and Hubbard prefer the term "idiosyncrasy," using it as a connotation for a temporary individual susceptibility to mercury intoxication, implying a lowered tolerance. They emphasise the many features of acrodynia common to subacute and chronic mercurial poisoning.

This theory of a temporary decrease in tolerance for mercury due to unknown factors established a useful working hypothesis, but is unfortunately clouded by reference to it as an "idiosyncrasy."

We found no evidence that acrodynia is an allergic response to mercury. The incidence of allergic disorders in acrodynia patients was about the same as in the general child population. There was no record of a second attack and no instance of eosinophilia in 97 investigated cases; there were only 1 positive patch test among 10 active cases, and 1 among 30 controls.

The regular ingestion of mercury as teething powders for many months before signs of pink disease develop is hardly compatible with its proposed rôle as an antigen. A poison can scarcely be credited with antigenic properties, because toxic reactions to it seem to vary with individual degrees of tolerance.

The disappointing results of treatment with dimercaprol, observed also by Warkany and Hubbard and by Denys (1950), again do not lend support to the idea that pink disease is an allergic phenomenon.

The 3 infants, however, who presented only some manifestations of pink disease after protracted ingestion of mercury, and whose raised serum-cholesterol level fell after the elimination of mercury, might be regarded as evidence of a toxic action on the kidneys preceding the more severe poisoning leading to nephrosis.

Cheek (1950, 1951) found lowered serum-sodium levels in patients with acrodynia, and suggested an underlying disturbance of adrenal function as causing pink disease. Williams et al. (1951) were unable to confirm Cheek's findings. The serum-sodium levels of 18 patients in the present series were examined, and only in 1 of them was the serum-sodium level abnormally low. None of these patients improved on treatment with salt, although some of the mothers thought the babies' emotional condition had improved.

SUMMARY

An attempt was made to study the relationship of mercury to pink disease, on the basis of (1) a follow-up study of 213 patients; (2) an inquiry into the habitual ingestion of mercurial teething powders among a cross-section of the healthy infant population of two regions varying in the incidence of pink disease; (3) the urinary excretion of mercury in acrodynia patients; and (4) the response to treatment with dimercaprol.

Of the 213 acrodynia patients seen during a twenty-year period 37 had died. Of the remaining 176 patients 110 were re-examined: 73% had developed normally; 27% were described as having minor psychosomatic disorders; and 50% gave a history of the ingestion of mercury.

The inquiry into the administration of teething powders to healthy infants in Salford and Manchester included 1561 babies, 109 (6·9%) of whom were habitually given mercurial teething powders. In the county of Warwick, of 1588 infants, 584 (37%) ingested more or less regularly mercurial teething powders.

The urinary excretion of mercury in 94 florid cases of acrodynia, studied during a three-year period, was abnormally high in 61 (65%).

The treatment of 15 cases with dimercaprol did not lead to any great improvement except in 3 cases, which are reported.

The high incidence of pathological excretion of mercury in active cases of pink disease, compared with the relatively low exposure-rate among healthy infants in the same region, is regarded as evidence that mercury is an ætiological factor in acrodynia, leading to chronic or subacute poisoning in infants with a low tolerance, probably in combination with other factors. The importance of other causal agents still unknown is not denied.

We wish to thank Prof. W. F. Gaisford, for his interest and valuable advice and permission to include in this study the patients under his care; Dr. C. Metcalfe Brown, M.O.H. for Manchester, Dr. J. L. Burn, M.O.H. for Salford, and Dr. S. W. Savage, M.O.H. for Warwickshire, and their senior assistants in charge of child welfare, Dr. Winifred Kane and Dr. M. Sproul, for their generous help in the survey; Miss V. K. Wilson, biochemist, Royal Manchester Children's Hospital, and Mr. H. Varley, biochemist, Manchester Royal Infirmary, for the estimations of urinary mercury; the visiting physicians of the Duchess of York Hospital for Babies, for their coöperation; and Dr. M. McGregor, consultant pædiatrician for Warwickshire, for the statistics of pink disease in that area.

REFERENCES

Baumann, T. (1949) *Schweiz. med. Wschr.* 79, 725.
Bivings, L., Lewis, G. (1948) *J. Pediat.* 32, 63.
Cheek, D. B. (1950) *Med. J. Aust.* i, 101.
— (1951) *Ibid*, i, 353.
Cosmi, S. (1930) Pink Disease (Infantile Acrodynia). Thèse de Paris, cited by Rocaz. C. London; 1933.
Denys, P. (1950) *Acta pædiat. belg.* 4, 16.
Elmore, S. E. (1948) *Pediatrics*, 1, 643.
Fanconi, G., Botsztejn. A. (1948) *Helv. pædiat. Acta*, 3, 264.
— — Schenker, P. (1947) *Ibid*, 2, 3.
Fisher, T. N. (1947) *Brit. med. J.* i. 251.
Jenny, E. (1930) *Schweiz. med. Wschr.* 60, 912.
Kromann, B. (1950) *Ugeskr. Laeg.* 112, 925.
Landolt, R. F., Egli, R. (1948) *Helv. pædiat. Acta*, 3, 272.
Lefebvre, G. (1949) *Arch. franç. pédiat.* 6, 82.
Loebenstein, F. (1949) *Ann. Pæd.* 172, 357.
van Creveld, S., Paulssen, M. M. P. (1949) *Acta pædiat.* 38, 82.
Warkany, J., Hubbard, D. M. (1948) *Lancet*, i, 829.
— — *Amer. J. Dis. Child*, 81, 335.
Watkins, C. G. (1950) *N.C. med. J.* 11, 188.
Williams, H., Macdonald, W. B., Callow, V. (1951) *Med. J. Aust.* i, 363.

ANÆMIA AND NITROGEN RETENTION IN PATIENTS WITH CHRONIC RENAL FAILURE

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The occurrence of normochromic anæmia in patients with chronic renal failure has long been recognised, one of the most complete studies of the subject having been made by Brown and Roth in 1922. Since then the anæmia has often been noted and several attempts made to explain it (see Callen and Limarzi 1950), but the ætiology remains unknown.

ÆTIOLOGY

Four mechanisms have been suggested: hæmorrhage, hæmolysis, hydræmia, and faulty hæmopoiesis.

Hæmorrhage.—Frank hæmorrhage occurs only in the final stages of uræmia and then not always; and hæmaturia, though sometimes present in the earlier stages, does not involve sufficient blood-loss to produce anæmia (Brown and Roth 1922, Roscoe 1950).

Hæmolysis.—Abnormal hæmolysis is not demonstrable by fragility tests or by an increased excretion of urobilinogen in most cases (Brown and Roth 1922, Loge et al. 1950); and, although there is sometimes evidence of an increased rate of destruction of transfused marked red cells, both Emerson and Burrows (1949) and Loge et al. (1950), who found this, decided that hæmolysis could at most be only a contributory cause.

Hydræmia is improbable when cases with œdema are excluded, since with progressive nitrogen retention dehydration tends to develop, and blood-volume studies by Harris and Gibson (1939) showed normal or reduced blood-volumes in patients with chronic nephritis without œdema.

Hæmopoiesis.—Failure of hæmopoiesis remains; and, although bone-marrow studies have not given clear-cut evidence of depressed red-cell production (Alexeieff 1937, Leitner 1949, Callen and Limarzi 1950) this appears the most probable mechanism. Even so it is not known why hæmopoiesis is slowed down. It can only be said that, when nitrogenous waste products accumulate in the blood, hæmopoiesis is depressed. This is not necessarily due to the excessive amounts of the measured products present, which may merely be indications of some other change producing the pathological effect. But if a definite relation between nitrogen retention and erythropoiesis is present it suggests that either the actual substance measured or some metabolite handled in a similar way is directly concerned.

RETENTION OF NITROGEN

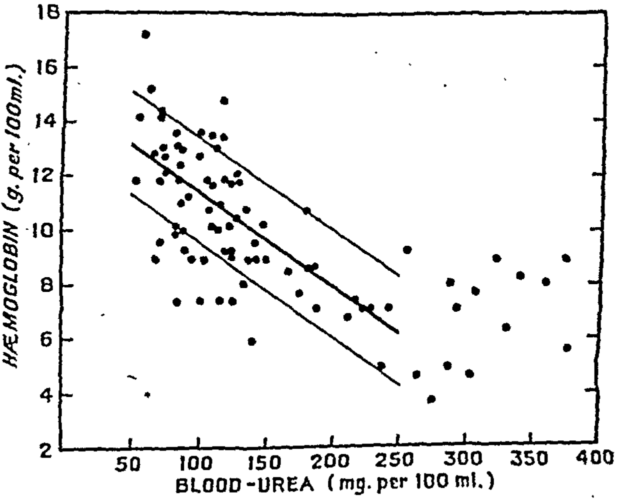
Correlation between hæmoglobin level and the level of urea, non-protein nitrogen, or creatinine in the blood was reported by Brown and Roth (1922), Townsend et al. (1937), and Callen and Limarzi (1950), but the cases studied were varied in type and the numbers not large; hence the absence of a quantitative relationship is not surprising. A further complication is that changes in hæmoglobin, due to bone-marrow failure, lag behind changes in nitrogen retention. This was noted by Brown and Roth (1922) and has led some workers to regard the duration of nitrogen retention as more important than its degree (Alexeieff 1937).

The results from 61 cases of chronic renal failure in which a quantitative relation between the hæmoglobin and blood-urea levels was apparent is therefore of interest. The failure was due to malignant hypertension, chronic type-1 nephritis, chronic pyelonephritis, or of unknown ætiology. No cases with œdema and hypoproteinæmia are included. In a few cases there was a hypochromic anæmia, with a colour-index below 0·90, but these results have been excluded because some complicating factor may have been present. To exclude as far as possible the error due to changes in hæmoglobin lagging behind changes in urea retention, values found when the blood-urea was known to have altered significantly in less than 50 days are excluded, and those obtained when the blood-urea was over 250 mg. per 100 ml. are considered separately, because at this level there is always a rapid increase in nitrogen retention.

The findings are plotted in the accompanying figure, which shows that, as the blood-urea rises from 50 to 250 mg. per 100 ml., the hæmoglobin steadily falls, but that, when the blood-urea is above 250 mg. the fall in the hæmoglobin does not continue. Mathematically the correlation for the 71 pairs of values between 50 and 250 mg. is good: $r = -0{\cdot}67, p < {\cdot}001$. The relationship can be expressed quantitatively by the regression equation of hæmoglobin on blood-urea, found by the method of least squares:

$$\text{Hb} = \left\{ 14{\cdot}8 - 0{\cdot}036\ (\text{blood-urea mg. per 100 ml.}) \right\} \text{g. per 100 ml.}$$

In other words the hæmoglobin tends to be 1·8 g. less for every rise of 50 mg. in blood-urea. There is, however, a considerable scatter in the results, the standard deviation from the regression line being ±1·9 g. Hb, hence no very accurate forecast of the hæmoglobin at any blood-urea level can be made. This is not surprising when the scatter of any series of normal hæmoglobins is remembered.



Hæmoglobin values at raised blood-urea levels. Thick diagonal line i regression line of hæmoglobin on blood-urea values between 50 and 250 mg. per 100 ml. Thin lines show standard deviation from regression line.

A further attempt to eliminate the effect of rapid changes in blood-urea was made by considering separately 28 of the cases in which the diastolic blood-pressure was 100 mm. Hg or less, since such relatively normotensive cases often remain with stable raised blood-urea levels for long periods. Here the fall is slightly greater, 2·2 g. Hb for every rise of 50 mg. in blood-urea, suggesting that, if in every case there had been time for the full effect of the raised blood-urea level to become apparent, lower hæmoglobin values would have been found.

SUMMARY

The hæmoglobin levels of 61 cases of chronic renal failure are shown to be quantitatively related to the blood-urea levels, falling as the blood-urea rises.

This suggests that the retention of some substance behaving like urea, may be responsible for the anæmia.

The hæmoglobin and blood-urea levels were estimated in the clinical laboratory of the Royal Infirmary, Manchester. I wish to thank Prof. R. Platt for advice and criticism.

REFERENCES

Alexeieff, G. (1937) *Sang*, 11, 972.
Brown, G. E., Roth, G. M. (1922) *Arch. intern. Med.* 30, 817.
Callen, I. R., Limarzi, L. R. (1950) *Amer. J. clin. Path.* 20, 3.
Emerson, C. P., Burrows, B. A. (1949) *J. clin. Invest.* 28, 779.
Harris, A. W., Gibson, J. G. jun. (1939) *Ibid*, 18, 527.
Leitner, S. J. (1949) Bone Marrow Biopsy. London.
Loge, J. P., Lange, R. D., Moore, C. V. (1950) *J. clin. Invest.* 29, 830.
Roscoe, M. H. (1950) *Quart. J. Med.* 19, 161.
Townsend, S. R., Massie, E., Lyons, R. H. (1937) *Amer. J. med. Sci.* 194, 636.

BORNHOLM DISEASE AND COXSACKIE VIRUS

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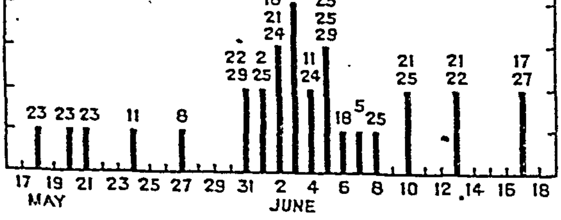
DURING the summer and autumn of 1951 numerous epidemics of Bornholm disease (epidemic myalgia) occurred in different parts of the British Isles. A preliminary report on a typical outbreak in Oxford (Davis and Warin 1951) led to correspondence in the *British Medical Journal* (1951) indicating that the disease had been prevalent in the Midlands, north-east England, and Scotland. There were similar epidemics in north-west England, and Coxsackie viruses were isolated in two of these, one of which is reported here. Hopkins (1950), after briefly reviewing the known facts about Bornholm disease, described 19 cases seen in his practice within two years.

Bornholm disease had been presumed to be a virus infection for some years, but until the Coxsackie or "C" group of viruses were isolated it was not ascribed to any definite ætiological agent. In 1949, Curnen et al. in the United States isolated a Coxsackie virus from a case of myalgia during an epidemic of aseptic meningitis associated with one of these viruses. In 1950, Weller et al. found an antigenically similar strain in a typical outbreak of Bornholm disease in the U.S.A. Coxsackie viruses have also been isolated during epidemics in Switzerland (Thelin and Wirth 1951) and in Israel (Bernkopf 1951). In Britain, too, Findlay and Howard (1950) and Giffin (1951) have established a relationship between Coxsackie virus and epidemic myalgia.

PRESENT OUTBREAK

The epidemic started in the middle of May, 1951, and was at first confined to one avenue of a new housing estate; it spread later to the surrounding area, but this report is concerned only with the localised outbreak.



Distribution of onset of symptoms during the epidemic.

The first three cases were in children from the same house, whose main initial symptom was abdominal pain. Two were admitted to hospital as surgical emergencies and one underwent appendicectomy. Two cases followed at 3-day intervals, and 4 days later the first two of the main group of cases became ill. The epidemic continued for another fortnight and then ceased abruptly. Sixteen families, consisting of 37 adults and 43 children, were investigated. Among these, 23 children and 7 adults, belonging to 14 families, were found to be affected; the distribution of cases is shown in the accompanying figure. The frequency of the various symptoms was as follows:

Clinical symptoms	*Age-group (yr.)* *0–15* *(23 cases)*	 *Over 15* *(7 cases)*
Pyrexia	20	3
Sore throat	12	4
Abdominal pain	20	5
Chest pain	0	2
Neck pain	1	0
Lassitude	5	0
Headache	3	5
Vomiting	10	2
Diarrhœa	7	1
Constipation	3	1
Shivering	1	2
Rash	1	0
Epistaxis	1	0
Convulsions	1	0

Two of the children with typical symptoms of Bornholm disease were admitted to hospital under the care of one of us (D. C. L.), and specimens from them were investigated for virus.

CASE-RECORDS

Case 1.—A girl, aged 4 years, admitted to hospital on June 6, 1951, with 3 days' history of abdominal pain, fever, and sore throat. On examination her temperature was 102°F, and her fauces and pharynx were injected, but no other abnormality could be found. Next day her temperature and throat were normal, and she remained well until her discharge on June 16.

RESULTS OF VIRUS STUDIES IN TWO CASES

Patient	Virus isolations		Serum neutralisation tests			
	Days after onset of symptoms	No. of mice infected/no. injected with fæcal extract	Days after onset of symptoms	Serum +100 I.D.$_{50}$ virus. No. of mice infected/no. injected at serum dilution of:		
				1 in 5	1 in 25	1 in 125
Case 1	7	6/6	5	5/5	6/6	—
	12	1/7				
	14	0/6	14	0/6	0/7	3/5
Case 2	9	0/6	7	0/6	6/6	—
	14	0/6				
	16	0/7	16	0/5	0/6	1/6

Case 2.—A boy, aged 4 years, admitted to hospital on June 6, 1951, with 6 days' history of abdominal pain, backache, sore throat, and shivering. On examination no abnormality could be found. He had no return of symptoms and was discharged well on June 16.

LABORATORY INVESTIGATIONS ON BOTH CASES

Blood-cultures were negative, and no pathogenic bacteria were isolated on cultures of throat swabs or fæces. Agglutination reactions with salmonella and brucella suspensions were negative.

One of the Coxsackie viruses was isolated (see table) from the fæces of case 1 by the technique used previously by Forrester and Tobin (1951). It was pathogenic for very young suckling mice only, its infectivity being markedly less in mice over 24 hours old. A fourth-passage inoculum containing a 10^4 I.D.$_{50}$ dose of virus for 18-hour-old mice did not affect mice which were 5 days old. Neither intracerebral nor intraperitoneal injections of virus produced any symptoms in 6-weeks-old mice, and no lesions were found when the virus was inoculated on the chorio-allantois of the developing chick embryo.

Histologically, the lesions in three suckling mice injected subcutaneously with a suspension of the virus were confined to muscle, fat, brain, and spinal cord. No lesions were seen in the liver, pancreas, or heart muscle. In skeletal muscle the virus produced a widespread myositis in one mouse, a very mild myositis in another, and no lesion in the third. The mouse with the diffuse myositis was the oldest of the three (36 hours, compared with the 18 hours of the other two) and it was obtained from a different dealer. All three showed some involvement of their adipose tissue, most pronounced in the large fat pads between the scapulæ and in the sucking pads; the most severe lesions consisted of necrosis and inflammatory changes starting at the periphery and spreading towards the centre of the lobules of the pads. In the brain and cord the lesions again varied in intensity: they consisted of areas of œdema and necrosis, vacuolation, pyknosis, and karyorrhexis of cells, and infiltration of the meninges with histiocytes and lymphocytes.

These findings place this Coxsackie virus in group B (Dalldorf 1951), which includes the strains associated with Bornholm disease in the United States. Whether it is of type B1 and so related to the Conn-5 strain of Melnick et al. (1949) and to the Demole strain of Weller et al. (1950) has not yet been determined. It was not neutralised by antisera prepared against group-A strains of types 1, 2, and 4.

Neutralisation tests with the sera of the two patients were performed in mice less than 24 hours old, and the results, shown in the table, indicate that both children had been recently infected with the virus isolated from one of them.

Attempts to isolate "C" virus from the sewer draining the affected area were unsuccessful 14 days after the epidemic had passed its peak.

DISCUSSION

Clinically this outbreak was typical of Bornholm disease, with severe pain affecting the abdomen and chest, pyrexia, and mild pharyngeal infection. More children were affected than adults. Involvement of the abdominal muscles was the outstanding feature of the epidemic; twenty out of twenty-three children and five out of seven adults complained of pain in this situation. The three children recorded as not having this symptom were all under 1 year of age. Tenderness and guarding were present in the lower abdominal quadrants during periods of pain, but between the attacks no abnormality could be found. Chest pain was present in only two patients, both adults. Eight patients had mild diarrhœa. No pathogenic bacteria were isolated from the fæces of the cases sent into hospital. Headache was more marked in the adults than in the children; there was no case of lymphocytic meningitis. The incubation period appeared to be 2–8 days.

The two cases shown to be infected with Coxsackie virus occurred during the epidemic of Bornholm disease. Their symptoms were typical of that disease, and there was no evidence that these two patients had some different illness than the remainder. The virus isolated belonged to the group in which other "C" viruses associated with Bornholm disease are found. If this strain is also antigenically related to them it will support the suggestion that epidemic myalgia is characteristic of one serological type of this group of viruses (Melnick 1951). This would simplify the routine diagnosis of this disease, especially in patients provisionally diagnosed as cases of lymphocytic meningitis.

SUMMARY

An outbreak of Bornholm disease is described in which a Coxsackie virus of Dalldorf's group B was isolated from the fæces of one of the affected patients. Serological evidence of recent infection with this strain was obtained in the two patients investigated, whose symptoms were typical of the epidemic.

Our thanks are due to Prof. A. C. P. Campbell for help with the histology; to Dr. M. M. Mackay for details of cases under his care; to Mr. A. Dixon, of the Rivers Department, for specimens of sewage; and to Dr. M. T. Parker, of the Public Health Laboratory, and the inspectors of the Health Department for their assistance.

REFERENCES

Bernkopf, H. (1951) *J. Amer. med. Ass.* 145, 1215.
British Medical Journal (1951) ii, 1089.
Curnen, E. C., Shaw, E. W., Melnick, J. L. (1949) *J. Amer. med. Ass.* 141, 894.
Dalldorf, G. (1951) Second Inte [illegible] *Conference*, Copenhagen, Symposium [illegible]
Davis, J. B. M., Warin, J. F. ([illegible]
Findlay, G. M., Howard, E. M. [illegible]
Forrester, R. M., Tobin, J. O'H. (1951) *Lancet*, ii, 663.
Giffin, T. (1951) *Brit. med. J.* i, 1185.
Hopkins, J. H. S. (1950) *Ibid*, i, 1230.
Melnick, J. L. (1951) *Ann. Rev. Microbiol.* 5, 309.
— Shaw, E. W., Curnen, E. C. (1949) *Proc. Soc. exp. Biol., N.Y.* 71, 344.
Thelin, F., Wirth, J. (1951) *Rev. Méd. Suisse Romande*, 71, 44.
Weller, T. H., Enders, J. F., Buckingham, M., Finn, J. J. (1950) *J. Immunol.* 65, 337.

FAMILIAL INTESTINAL POLYPOSIS WITH PIGMENTATION OF LIPS, ORAL MUCOSA, FACE, AND DIGITS

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Jeghers et al. (1949) draw attention to a rare familial disorder in which melanin pigmentation of the lips and oral mucosa and, in some cases, of the face and digits is associated with polyposis of the gastro-intestinal tract, especially the small intestine. These workers report 10 cases of this syndrome seen by them in America and mention 3 others. In addition they review 12 proven and 5 probable cases recorded by other authors. Among the latter were two twins originally reported by Jonathan Hutchinson (1896) because of unusual black pigmented areas on the lips, oral mucosa, and face. Subsequently Parkes Weber (1919), in an article on pigmentation of the buccal mucosa not associated with Addison's disease, stated that one of these twins had died of intussusception at the age of 20. The first proven cases of the complete syndrome, affecting several members of the same family, were reported from Holland by Peutz (1921). In this country

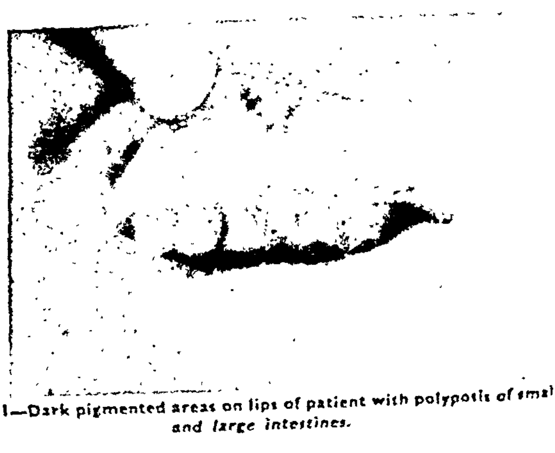

Fig. 1—Dark pigmented areas on lips of patient with polyposis of small and large intestines.

Foster (1944) described the cases of a father and daughter both of whom had had an intussusception caused by a polyp of the small intestine and both of whom showed dark pigmentation of the lips and face. A further case of the complete syndrome has been reported in this country by Tanner (1951). This brings the total of proven cases of this syndrome hitherto published to 26. I report another case here.

CASE-RECORD

A man, aged 50, was admitted to St. Helier Hospital in August, 1951, with six weeks' history of repeated attacks of abdominal pain. Each attack was of sudden onset, lasted several hours, and was accompanied by gurgling noises in the abdomen and by nausea. During one of them the patient's doctor had felt a lump in the right iliac fossa; it varied in size during the attack.

The patient gave a history of similar recurrent attacks of abdominal pain between the ages of 17 and 23. At the age of 20 his appendix was removed, but the attacks continued. A few months later he came under the care of Mr. Zachary Cope, who operated on him four times in a month because of recurrent intussusception of the small intestine caused by multiple polyps. Several of these polyps were removed individually without resection of the gut. An account of these operations was given by Cope (1922), but the dark pigmentation on the patient's lips was not noted at the time. Two years later the patient had a further attack of intussusception, and a portion of small intestine containing numerous polyps was resected. After this operation he had no further symptoms until six weeks before the present admission.

Family History

The patient had had five children, of whom four were alive.

One son had died in 1939, at the age of 5 years, after an operation for intussusception. He had had several attacks of abdominal pain during the year preceding the operation. The parents had noticed that he had on his lips and face several dark spots which had been present since birth, but had increased subsequently. These had been similar to areas of black pigmentation which the present patient had had on his lips since early childhood (fig. 1).

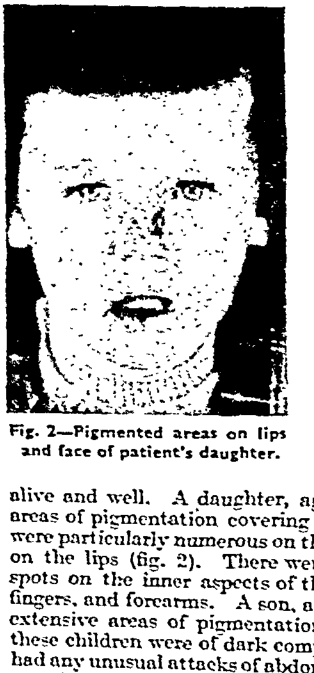

Fig. 2—Pigmented areas on lips and face of patient's daughter.

The other four children were alive and well. A daughter, aged 5, had many dark-brown areas of pigmentation covering her face and forehead. These were particularly numerous on the nose, round the mouth, and on the lips (fig. 2). There were several similar dark-brown spots on the inner aspects of the cheeks and on the thumbs, fingers, and forearms. A son, aged 16, had similar though less extensive areas of pigmentation on his face and lips. Both these children were of dark complexion. Neither of them had had any unusual attacks of abdominal pain. The other children, two boys aged 8 and 2, had no abnormal pigmentation although the elder had several pale-brown freckles on his face.

The patient's parents were both dead and, so far as could be ascertained, had not had any abnormal pigmentation or intestinal symptoms. They had *not been related*. The patient had four sisters and a brother who were said to be unaffected.

Condition and Findings

On admission it was noted that there were several irregular patches of dark pigmentation on the patient's lips (fig. 1) and a few smaller patches on the inner surface of his cheeks. There were also a few scattered dark-brown spots on his face, distributed mainly round his mouth, and a few similar dark spots, 1 mm. in diameter, on several of his fingers and on his forearms. The patient's complexion was dark. Except for several operation scars on the abdomen, physical examination revealed no other abnormality. His blood-pressure was 120/70 mm. Hg.

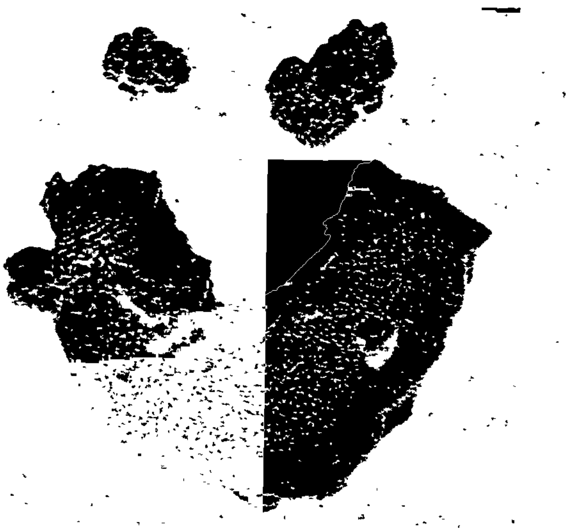

Fig. 3—Two large polyps removed from duodenum and sigmoid colon, and portion of jejunum containing several sessile and pedunculated polyps.

In hospital he had several further attacks of abdominal pain. During some of these a mass of varying size could be palpated in the right iliac fossa, and there was visible peristalsis of the small intestine. A barium meal and a barium enema failed to show any definite abnormality, although there were in the small and large intestines a few irregular translucent areas which suggested filling defects. Sigmoidoscopy revealed two small polyps in the rectum and a larger polyp in the sigmoid colon. The hæmoglobin was 65%. A white-cell count was normal.

Operation

Operation was performed by Mr. York Mason on Aug. 21, a few hours after the onset of another severe attack of abdominal pain. No polyps could be palpated inside the stomach. A large polyp was felt inside the beginning of the jejunum. Its pedicle arose from the second part of the duodenum; after the polyp had been returned to the duodenum, this was opened and the polyp was removed. Several other polyps were palpated in the proximal portion of the jejunum. These were left in situ. Distal to these, two separate portions of the small intestine, greatly dilated and hypertrophied, were resected and found to contain several sessile and pedunculated polyps (fig. 3). One of these had been responsible for the recent attack of intestinal obstruction. At the site of the obstruction the small intestine was firmly adherent to the bladder wall and had to be separated from it before the affected coils of intestine could be resected. A few small polyps were palpated inside the ascending colon. These were left in situ, but one large polyp, causing a small intussusception, was removed from the sigmoid colon. After the operation the patient made an uninterrupted recovery. Histological examination confirmed that the tumours were simple adenomatous polyps.

DISCUSSION

This case illustrates all the essential features of this rare syndrome:

(1) *Pigmentation*, from birth or early childhood, on the mucosa of the lips and, in some cases, also inside the mouth and on the face and digits. This has been shown to be due to deposits of melanin (Jeghers et al. 1949), and all the patients with this syndrome reported so far have been of dark complexion.

(2) *Multiple polyps*, in the same patient, of the gastro-intestinal tract. The small intestine has been involved in every case, and polyps have been present in the large intestine in most of the cases. In 5 of the 10 cases described by Jeghers et al. (1949) and in the case described by Tanner (1951) polyps were also found in the stomach. Symptoms are usually due to repeated attacks of small-intestine obstruction caused either by a large polyp or by an intussusception. In 1 of the cases of Jeghers et al. (1949), in 2 members of the family

described by Peutz (1921), and possibly in the 2 cases described by Foster (1944) there was evidence of malignant change in one of the small intestinal polyps.

(3) *Familial Incidence.*—There is a strong tendency for several cases of this syndrome to occur in the same family, some members of the family showing the complete syndrome of intestinal polyposis and pigmentation, and others the pigmentation only (Touraine and Couder 1946, Jeghers et al. 1949). Possibly some of the latter may have had intestinal polyps which had not produced any symptoms. In the present case the father showed the complete syndrome. One son, who had the characteristic pigmentation, died of intussusception, and, although no further data of this case are available, it is reasonable to presume that this was also due to an intestinal polyp. Two other children have the pigmentation but have so far remained free from abdominal symptoms. Families have also been reported in which several members showed the characteristic pigmentation but none presented any evidence of intestinal polyposis (Touraine and Couder 1946). Conversely, either generalised or small-intestinal polyposis can occur without any associated pigmentation (Ravitch 1948), but possibly in some of these cases the pigmentation was overlooked or its significance not recognised, as happened when the present case was first published thirty years ago (Cope 1922).

In spite of its rarity this syndrome is of clinical importance, because the dark pigmentation on the mucosa of the lips and mouth, in a patient without Addison's disease and with a history of attacks of abdominal pain strongly suggests polyposis of the small intestine.

SUMMARY

A case is described in which pigmentation of the lips, oral mucosa, face, and digits was associated with numerous polyps in the small and large intestine. This association constitutes a rare but definite syndrome which, as in the present case, may affect several members of a family.

I wish to thank Mr. A. York Mason, under whose care the patient was admitted, and Dr. J. B. Harman for permission to publish this case; Mr. Zachary Cope for details of the previous operations; and Dr. W. G. Millar for the photographs.

REFERENCES

Cope, Z. (1922) *Brit. J. Surg.* 9, 558.
Foster, D. B. E. (1944) *Brit. med. J.* ii, 78.
Hutchinson, J. (1896) *Arch. Surg.* 7, 290.
Jeghers, H., McKusick, V. A., Katz, K. H. (1949) *New Engl. J. Med.* **241**, 993, 1031.
Peutz, J. L. A. (1921) *Ned. Maandschr. Verlosk. (Geneesk.)* **10**, 134.
Ravitch, M. M. (1948) *Ann. Surg.* **128**, 283.
Tanner, N. C. (1951) *Proc. R. Soc. Med.* **44**, 405.
Touraine, A., Couder, F. (1946) *Pr. méd.* **54**, 405.
Weber, F. P. (1919) *Quart. J. Med.* **12**, 401.

Medical Societies

ROYAL SOCIETY OF MEDICINE

Psychologist's Rôle in Psychiatry

THE psychiatric section of the Royal Society of Medicine met on Feb. 12, under the chairmanship of Dr. DESMOND CURRAN, president of the section, to discuss the rôle of the psychologist in psychiatric practice.

Dr. HENRY WILSON admitted that he was somewhat reactionary as regards psychologists, perhaps regarding them rather as the general physician at the beginning of the century would have regarded the alienist. He divided psychiatric practice into three aspects: diagnosis, treatment, and research. In diagnosis the psychologist could help in dealing with children, whose problems of behaviour might be unravelled with test procedures, such as the measurement of handedness and unequal development of skills. He cited the work done on recognition of infantile schizophrenia and its separation from mental defectiveness. With adults, he felt that "social dexterity," by virtue of which some people with intelligence well below average achieved success in their community, was too often overlooked. He did not think that the psychiatrist should ask for too many psychological tests as a routine; he should rely more on his own clinical judgment, using tests for confirmation and not to give fictitious weight to a psychiatric "protocol." In treatment, he felt that an intuitive psychologist could be very helpful in re-educating adults with organic cerebral diseases. The Rorschach and the thematic apperception tests were of doubtful value in diagnosis, but were often useful in getting the patient to start talking. In research, he felt that there was work to be done by the psychologist on the characteristics of memory loss after electroconvulsive therapy. Closer attention should be given to the dysphasias—which were much commoner than was generally realised—and to the factors of nature, nurture, and training in the formation of the epileptic personality; and much more should be learnt about the results of leucotomy. In all these subjects the psychiatrist needed the accuracy of the psychologist to help him.

Mr. O. L. ZANGWILL said that there were two main sources of misunderstanding between psychiatrist and psychologist. The psychiatrist was always demanding more standards of mental assessment whereas the psychologist was impatient of this narrow field and wanted to work in the clinical sphere. He felt that psychiatrists were too often overawed by quantitative mental tests, to which they attached a finality and validity not always claimed by the psychologist. Such tests were rather pragmatic and tentative and should not be interpreted as strict measuring instruments. They needed to be applied in the light of clinical experience. In post-leucotomy studies, for example, there was a tendency to base tests on preconceived dimensions of personality, rather than to discover the postoperative changes, by the methods of clinical observation, and then devise tests to demonstrate such changes better.

The nomenclature employed by psychiatrist and psychologist also created misunderstandings. There were, one might say, *two* psychologies. In much psychiatric writing, terms were used in their lay sense [illegible] ch a special meaning. [illegible] " meant a general [illegible] with such symptoms [illegible] *ereas to the psychologist* it meant a discrepancy between certain test measures. Then again, psychologists like *Eysenck*[1] had defined concepts such as "suggestibility" and "neuroticism," which did *not* necessarily earmark the hysteric or the neurotic in whom the psychiatrist would expect to find them most strikingly exemplified. Joint discussion of clinical and psychometric findings could, however, be rewarding if misapprehensions were cleared away.

In research, he felt that the psychologist's rôle was additive. The psychiatrist could assess mental phenomena from the *clinical* angle, while the psychologist applied batteries of tests in the hope that something else would emerge and be correlated with the clinical findings. Coöperative research of this sort required more than juxtaposition, more than working in the same building: a common background of training and understanding was necessary. Hitherto psychology and neurology had collaborated more closely than psychology and psychiatry. The trouble was largely due to the *two* psychologies, that of the psychiatrist being academic and expressed in terms of emotions and mental dynamics, while that of the psychologist was objective and statistical.

Mr. H. J. EYSENCK, PH.D., said that the psychologist had the choice of two rôles in psychiatric practice: that of technician or that of scientist. Some psychologists seemed unable to decide between the two, but he felt it was impossible to have it both ways. The technician rôle was especially common in current American practice: he felt it gave rise to the minimum contribution from psychology to psychiatry and created the maximum friction. It involved the psychologist's acquiescence in the conceptual system of the psychiatrist, which was usually implicit rather than explicit, and his endorsement of methods of psychotherapy whose effectiveness was not supported by follow-up studies. As therapy was the most prestige-giving rôle, the psychologist tended to invade it; and this created friction with the psychiatrist, and sacrificed the objective, scientific approach to the problems of therapy. As a scientist the psychologist should be complementary to the psychiatrist, not his imitator; and for this he must renounce therapeutic ambitions. The psychologist needed the psychiatrist's intuition and clinical observation; for his part, he could contribute accuracy and definition, with mathematical and statistical checks of the psychiatrist's hypotheses.

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[1] Eysenck, H. J. Dimensions of Personality. London, 1947.

The routine administration of psychological tests was of very little use; an alternative method of clinical work, more closely integrated with the scientific training of the psychologist, had been suggested by some psychologists.[2] Division of function between psychologist and psychiatrist could lead to truer coöperation and a more fruitful brand of collaboration.

Prof. ALEXANDER KENNEDY expressed general agreement with the previous speakers. He wished, himself, to draw some conclusions and to discuss the future of the relationship between the two disciplines. Psychiatry was a branch of medicine, and must depend on human and intuitive qualities and clinical skill if it were not to become dehumanised. The scientific efficiency and detachment of the psychologist were also needed. There was a difference in background between the psychiatrist and the psychologist: too often the psychiatrist regarded statistics as the work of the Devil, while the psychologist gave the impression of regretting that all mankind was not composed of uniovular twins. He paid a tribute to the British Psychological Society for its work in raising the standards of psychological training. There was still need for the psychologists to obtain uniform training at the various universities in this country. He hoped that there would emerge a code of ethical conduct among psychologists, both in their contact with the patient and in their public relations. The public was still very ignorant of the psychologist's function.

The psychologist could not be expected to give his best help unless he enjoyed better facilities for training in coöperation with medical men. He should have access during training to neurophysiological departments and clinical material. This was being arranged at Durham University, where psychologists and medical postgraduate psychiatric students had part of their training in common; he had found that dissection of the brain together was especially valuable as a means of informal contact. On the other hand, the psychiatrist should have more access during training to normal material; he should learn about children from normal schools rather than from clinics. Professor Kennedy felt that the psychologist could teach the psychiatrist much, especially in industrial psychology; and he was himself prepared to delegate certain formal therapeutic rôles to those who worked with him. The future of clinical psychology lay in increased contact and collaboration between both partners.

Dr. W. MAYER-GROSS agreed with Mr. Zangwill about the "two psychologies." It was quite remarkable how two such related subjects as psychiatry and psychology had developed, not along parallel lines, but in complete divergence except for their contact in occasional personalities. He did not agree that the psychologist should undertake therapy: he should refuse to emulate the psychiatrist, and the psychiatrist should equally refuse to be deterred by the psychologist's statistical methods from making use of his services.

Reviews of Books

Genetics of Micro-Organisms

D. G. CATCHESIDE, reader in plant cytogenetics, University of Cambridge. London: Pitman. 1951. Pp. 223. 21s.

IN recent years micro-organisms have become pre-eminent as material for experimental genetics. Since they are easily cultivated in large numbers on defined media, are rapidly generated, and present a metabolism comparable with that of mammalian cells, they have considerable advantages over the traditional fruit-fly and corn-plant. The possibilities of genetic analysis are probably maximal with fungi (in genera like neurospora, for instance, the products of meiosis can be recovered separately and studied in haploid form); and more work has been done with these than any other microbes. Hence the early chapters of this book give an account of the principles, methods, and results of neurospora studies. Dr. Catcheside discusses clearly the nature of mutation, gene action, and adaptation, and shows how genetics allied to biochemistry is helping to define the steps of intracellular metabolism. Yeasts, protozoa, bacteria, and viruses have a chapter each, and readers will enjoy the discussion on transformation, modification, and plasmagenes. Cytoplasmic particles, probably existing in all cells as plasmagenes, are self-reproducing and help to determine the character of the cell, yet are not gene-initiated, nor subject to Mendelian inheritance. Indeed they often behave like viruses, and may perhaps at times *be* viruses. They are certainly sensitive to changes in the environment, and their loss or gain or mutual competition can be influenced by the experimenter, so that he has some degree of control over the expression of inheritable character.

This book has been long awaited by biochemists, microbiologists, and those engaged in cancer research: it is concisely written by a well-known authority, and is the only work of its kind. Within a few weeks of publication it is already to be seen, thumbed and annotated and with its jacket off, on many desks.

Markpagelung nach Küntscher

Bei Schaftbrüchen der langen Röhrenknochen (2nd ed.) Prof. Dr. CARL HÄBLER, Hanover. Munich-Berlin: Urban & Schwarzenberg. 1950. Pp. 302. D.M. 26.

L'ostéotaxis

Ostéosynthèse transcutanée par fiches et rotules. Dr. RAOUL HOFFMANN. Paris: Editions Gead. 1951. Pp. 161.

THESE two books bring to mind Kipling's famous dictum on the construction of tribal lays; there are very many ways, it seems, of reducing and fixing fractures by the introduction of metal into bone, "and every single one of them is right"—at least in the hands of a single-minded and enthusiastic advocate. Professor Häbler's account of medullary nailing is based on experience of the end-results in over 900 cases, many of them war injuries. He gives clear instructions for the nailing of each of the limb bones, setting out in great detail the armamentarium and operative technique in each instance—with a preference for closed nailing from a distance. What he does not make so clear are the precise indications for using Küntscher's method rather than conservative, or an alternative form of operative, treatment. Nevertheless, he is well aware of the limitations and dangers of the method, and makes it plain that surgeons who use it with imperfect equipment and technique are asking for trouble.

Dr. Hoffmann transfixes each fragment of a fracture with several pins, each group of pins being locked into an external metal unit, and the two units clamped rigidly to a metal connecting bar. He does not claim more for his method than that it fills a gap in standard conservative treatment, and is a useful adjunct when open operation proves necessary; and though one suspects that he uses it with considerably more freedom than that, it is obviously capable, in careful hands, of giving excellent results. However, osteotaxis seems to resemble the essentially similar technique (which Dr. Hoffmann claims to be more recent than his own) introduced by Stader in the United States for providing a temporary exoskeleton; and it carries the same risk of producing annular necrosis and sequestration, and of tethering muscles at the points of transfixion—risks which impressed British observers of this American method during the war. Osteotaxis and medullary nailing have one thing in common which make them relatively unpopular in this country: the fracture is reduced and fixed under fluoroscopic control whenever possible. Indeed, this is essential to Dr. Hoffmann's technique, which is therefore unlikely to be widely adopted here. The same difficulty had to be overcome with medullary nailing, which we have accepted, not in its original form, but as an open procedure with retrograde nailing under direct vision.

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[2] Shapiro, M. B. *J. ment. Sci.* 1951, 97, 748.

Human Physiology

With Essentials of Histology, Biochemistry and Biophysics. C. C. CHATTERJEE, M.D., B.SC., formerly of the physiology department, Medical College, Calcutta. Calcutta: U. N. Dhur & Son. 1951. Pp. 813. 45s.

IN the preface Dr. Chatterjee implies that his book is not intended as an "aids" or cram book. On the other hand, he states that "a good deal of attention has been paid to assure success in examinations." To this end he has divided his account of the systems into a number of short sections and subsections in the way that he thinks will best answer questions likely to be set by various examining bodies in India and elsewhere; and the result, unhappily, *is* a cram book. The student with a good knowledge of physiology might perhaps refresh his memory by glancing at the headings, but many statements are so compressed that an ignorant reader would be led to the wrong conclusion. To combine a textbook of physiology with a guide to the answering of examination questions is to dispense a mixture of incompatibles, and it is not surprising that the result is disappointing.

La tuberculosis traqueobronchopulmonar

LUIS SAYÉ, late professor of phthisiology, the Faculty of Medicine, Barcelona. Buenos Aires: Guillermo Kraft. 1951. 2 vols. Pp. 598 and 599.

Professor Sayé became interested in the bronchial lesions in pulmonary tuberculosis in 1936, and since then has given special attention to them, both bronchoscopically and at post-mortem examination. These studies were started in Barcelona, and continued in Buenos Aires. As a result of them, he has written a comprehensive account of the clinical and pathological manifestations of tuberculosis in the respiratory system from a new viewpoint.

In the standard descriptions of the pathology of pulmonary tuberculosis, the pulmonary lesion is given precedence, and bronchial lesions, apart from those associated with ulceration of the lymph-node component of the primary complex into a bronchus, are regarded as secondary, and mentioned as a sort of addendum to the main description of the pulmonary lesions. This is not surprising, since the standard descriptions are based upon post-mortem evidence only, and have not been much influenced by the more recent observations on the pathology of the living, derived from bronchoscopic studies, from the examination of surgical specimens, and to some extent by inference from radiography. The textbooks in this, as in other matters, inevitably lag behind the best current practice; for the extreme importance of the bronchial changes in tuberculosis of the lower respiratory tract is, of course, fully recognised by physicians interested in respiratory disease.

The book is well described by its title "Tracheo-broncho-pulmonary tuberculosis"; it treats tuberculosis of the lower respiratory tract for the first time in an integrated manner, not regarding bronchial lesions as "complications," but as an essential and important part of the pathological process in a very high proportion of cases. The new terminology which Professor Sayé has developed as a result of this approach may seem unnecessarily detailed, and it certainly makes the presentation of his views rather complicated; but his classification will be found to correspond with the [illegible] facts, and his nomenclature, though [illegible]ersome, is readily comprehensible.

It is refreshing to be reminded that the combination of clinical and morbid anatomical approaches can still add so much to our understanding of disease. The fact that Professor Sayé writes in Spanish should not dissuade anyone without a knowledge of that tongue from studying it, since the illustrations are numerous and of reasonably good quality, and anyone with a knowledge of Latin and French should be able to understand the text.

Gestalt Psychology: Its Nature and Significance

DAVID KATZ, PH.D., professor of psychology, University of Stockholm. Translator: ROBERT TYSON, PH.D. London: Methuen. 1951. Pp. 175. 12s. 6d.

GESTALT psychology is not as eagerly pursued in this country as it was thirty years ago. Its achievements were solid, but they have proved arid and baffling to a generation more interested in motivation than in perception. In this authoritative but critical work, now made available in an English translation (with some new chapters on mental work and the transposition of action-forms), Professor Katz indicates how wide was the scope of gestalt psychology and how, in his own hands and those of Lewin, Goldstein, and others, it extended into many fields of application, some of which have much medical interest. The account is clear and well organised, and suffers only from the inevitable consequences of compressing so much painstaking research into a brief space: the Leipzig school suffers particularly.

Man into Wolf

An Anthropological Interpretation of Sadism, Masochism and Lycanthropy. ROBERT EISLER. London: Routledge & Kegan Paul. 1951. Pp. 286. 21s.

THIS book is written around a lecture delivered to the psychiatric section of the Royal Society of Medicine. The lecture occupies a ninth of the book; the rest is exposition and citation of authorities. The effect of the whole is somewhat like that of the *Anatomy of Melancholy*: so much erudition is brought in to support a diffuse and improbable theme that the reader is bogged down in curious detail, and becomes more interested in the style than in the thesis. The main argument is that modern man is descended from harmless vegetarian primates, who acquired predatory lusts through mating with a carnivorous lycanthropic variety of man who imitated the aggressive savagery of wolf packs. Hence the strange contrasts in our nature and, in Dr. Eisler's view, the possibility of reversion to the peaceful ways of sylvan ancestors. The references to C. G. Jung's doctrine of archetypes and the traces of Dr. Eisler's earlier studies of the Orphic cult are numerous throughout the book.

Chemotherapy of Cancer: *The Inaugural Florence Blair Bell Lecture to the Liverpool Medical Institution* (Liverpool: University Press. 1951. Pp. 31. 2s. 6d.).—The title of this booklet is the pretext; the real purpose of the lecture being to eulogise William Blair Bell, as Sir Stanford Cade explains at the outset. Much of the text therefore deals with the most important events of Blair Bell's life, and with his work; only six pages are allotted to a survey of the place of chemotherapy in the control of malignant disease in 1950. The booklet ends with the first really complete bibliography of Blair Bell's writings.

Hypertension (Minneapolis: Minnesota University Press. London: Oxford University Press. 1951. Pp. 573. 60s.).—This volume, edited by Dr. E. T. Bell, represents the proceedings of a symposium on hypertension held at the University of Minnesota in the autumn of 1950. It consists of thirty papers by 24 workers of international repute writing largely on their own work. They summarise existing knowledge and current opinion in a difficult field and leave the reader to form his own conclusions. The subject-matter is largely available in current medical journals, but many will be grateful to find the information conveniently assembled in one volume.

THE LANCET

LONDON: SATURDAY, MARCH 1, 1952

Economy in Hospitals

> "You will know from the recent Debates in Parliament how serious is the financial position of our country. As Minister of Health I have a duty to see that expenditure in the Hospital Service is kept as low as it can be without failure to meet the needs of the patient, and that every pound that is spent is wisely and not wastefully spent . . . I would urge that a special review should be made at once to see whether there is not room for further economy, however small."

So runs a letter from Mr. Harry Crookshank to all chairmen of hospital boards and committees; and everywhere medical staffs have been asked for their coöperation in fulfilling its object. Though the hospital services have shown little evidence of gross extravagance or waste, they certainly offer scope for economy in the sense of good housekeeping, and it is entirely reasonable that consultants and specialists should be urged to do all they can to ensure that money is indeed well spent. Unfortunately, as has so often been pointed out, the method by which hospitals have been financed, on a rigid system of budgeting, has removed normal incentives to economy instead of strengthening them, and in this respect there is room for much further improvement, particularly the trial of new methods such as the "block allocation." Meanwhile the pressing need is for a careful review of the hospitals by those intimately concerned in their work.

From the viewpoint of the public, a major contribution to economy can be made by securing a more rapid turnover of acute cases. The average stay in "acute" hospitals varies between 11 and 24 days, and if the average stay were reduced by only 1 day the present waiting-lists could be largely cleared. It is vital that whatever measures are introduced in the name of economy should not reduce the turnover of patients. To deal with more of them in a given time is bound, however, to increase expenditure on medical investigations, and it is here that the medical staff can make their maximum contribution by countervailing economy in the use of their resources. A more efficient use of hospital beds could be achieved by linking acute hospitals more closely with convalescent centres: beds related to the expensive ancillary services should be reserved for those who still need them. As was made evident by the report published last year by King Edward's Hospital Fund for London, patients are kept in hospital waiting for beds in convalescent homes while the homes themselves often have empty beds. What is particularly needed is a dovetailing of convalescent homes with a parent hospital, enabling them to serve as convalescent hospitals rather than convalescent homes.

In any large organisation it is almost always possible to do more to reduce waste to a minimum. Much of one's daily activity is governed by methods which have been long in use, and a critical review will often show how the same amount of work can be done using less material. Dr. E. P. Joslin, when visiting a diabetic clinic in this country, asked a young diabetic patient how she tested for sugar in the urine, and was correctly told: he commented drily that in his country they used half the amounts. Of late years there has been much routine prescribing of expensive vitamin preparations, and a committee of the Liverpool Regional Hospital Board noted that in the year ending last March vitamin preparations absorbed 4·48% of the board's expenditure on drugs —a figure which it was felt could be explained only by indiscriminate and unnecessary prescribing. In another region a large municipal hospital found that the salary of a dietitian would be comfortably covered by discontinuing the routine prescription of vitamins to all patients admitted—a practice begun by a previous generation of housemen and in some wards continued with the knowledge of the consultants. The large gallipot of spirit or iodine liberally dispensed by the junior nurses for a simple venepuncture probably represents a tenfold excess of antiseptic required. Multiplied many times a day in every hospital throughout the country, this must represent an enormous waste. The Liverpool committee suggests that periodically a short list be displayed in the residents' room and sisters' room showing the current prices and local consumption of items of medical supplies. At least one hospital pharmacy department has organised a small exhibition to show the cost of common drugs and has demonstrated how easily reasonable economies can be made. Those working full-time in hospitals—i.e., housemen, registrars, and 1500 of the 5500 consultants—have had little opportunity of learning in private practice the cost of modern expensive antibiotic or hormone preparations. It has been an inestimable benefit to patients that these drugs have been freely available regardless of cost, but senior members of the staff ought to make sure that such treatment is cancelled as soon as the indication for it has passed. All of us, of course, are apt to be unaware of errors in our own routine which would at once be apparent to an independent observer, and it might be possible for hospital management committees and their medical committees to make a habit of obtaining candid criticisms from an independent organisation or from another board or H.M.C. The advisory service of King Edward's Hospital Fund has done much to improve catering and eliminate waste in hospitals, both by inspection of individual hospitals and by informative circulars.

In the National Health Service part-time consultants are paid their travelling expenses and are also paid for the time of their journey. Under this arrangement it is financially desirable that consultants should have their hospital appointments mainly in one area—for example, mainly within one management-committee area—thus reducing the present multiplicity of consultants attending one hospital management group. A rational redistribution of work on these lines is in practice difficult to secure; but the movement is one that should receive support from consultants, if they wish to justify the existing state of payment for travelling time, which is a source of uneasiness among the non-medical administrators. The expenditure involved is not inconsiderable: indeed in one group of three large hospitals in London it has been calculated as equivalent to the salary of seven full-time consultants. Redistribution of consultants is desirable not only for financial reasons but also to improve the organisation of medical services within hospital groups.

The real cost of hospital services has not yet been met. An examination of the figures from different regions suggests that many millions of pounds are needed even to bring the rest of the country up to the standard of the four Metropolitan regions, where the optimum is still far from attainment.[1] With rising costs, with steadily increasing claims for hospital outpatient treatment, and with medical investigations increasing in complexity, it is evident that the present ceiling of expenditure will have to be raised in due course, if the public are to continue to receive the service that the profession would wish them to receive. But further claims on the Treasury will undoubtedly be resisted unless there is clear evidence that the Minister's request for economy has been heeded and that value is obtained for every pound. Hence the consulting staff should feel that their personal responsibility extends not only over the welfare of their patients but also over the administrative economy of their own unit. The incentive to economy should properly start at the top and permeate down to the most junior member of the medical team.

Infective Hepatitis and Cirrhosis of the Liver

DESPITE advances in our knowledge of the pathogenesis of liver diseases, the cause of hepatic cirrhosis is still undecided. Formerly alcohol was considered the pre-eminent cause; but often this agent can be excluded with certainty—for example, in young children, and in communities where consumption of alcohol is prohibited on religious grounds.

The insistence by MALLORY [2] in 1911, and by many workers since then, that hepatic cirrhosis is not an entity but the end-stage of several distinct processes has helped to clarify the problem. Excluding biliary cirrhosis due to long-standing obstruction of the bile-ducts, three factors are today held to be significant: exposure to so-called liver poisons, deficiency of certain specific nutriments, and a previous attack of infective hepatitis. The three factors are closely interdependent, which no doubt accounts both for the difficulty in unravelling the precise importance of each, and for the differing opinions of their relative importance. Before the late war work on the relation of nutrition to liver diseases was concerned mainly with the influence of dietary factors on susceptibility to exogenous liver poisons. That deficiency of specific food factors in the absence of known liver poisons can itself lead to hepatic necrosis and cirrhosis is a fairly new idea, based particularly on the experimental work of GYÖRGI and GOLDBLATT,[3] DAFT et al.,[4] and HIMSWORTH and GLYNN,[5] and the clinical studies of TROWELL,[6] WATERLOW,[7] and the GILLMANS.[8] In the Western Hemisphere, however, with its higher standard of living, a purely dietary cause is less likely, and HIMSWORTH and GLYNN suggested the possibility of a secondary or conditioned deficiency. Nevertheless, many observers have felt that neither exogenous toxins nor primary or conditioned nutritional deficiency could account for the observed incidence of hepatic cirrhosis, and have brought forward evidence that many of these cases are the late result of infective hepatitis.[9] The great majority of hepatitis patients apparently recover completely in a few weeks. A small proportion die from massive hepatic necrosis. In yet others the disease appears to remain active for several months, and the histological appearance of the liver suggests progressive parenchymal destruction and fibrosis, which might be expected to progress to Laennec cirrhosis. A few patients, especially those recovering from an extremely severe attack, develop the typical clinical and anatomical picture of so-called "toxic cirrhosis"—i.e., nodular hyperplasia with post-necrotic scarring. HIMSWORTH and GLYNN postulated, on theoretical grounds, that both types of cirrhosis might follow infective hepatitis, the Laennec type owing to persistent or recurrent activity of the disease, the post-necrotic type as a sequel to massive necrosis due to associated malnutrition. While most workers agree that infective hepatitis may lead to the "toxic" form of cirrhosis, few have reported that it may lead to typical Laennec cirrhosis.[10]

The striking differences in the severity of the disease may be due to variations in the virulence of the causative virus; but this cannot at present be verified or disproved. The great differences in mortality, however, in epidemics in different parts of the world indicate the important influence of nutrition on the prognosis: in the outbreak of homologous-serum jaundice that followed the early use of yellow-fever vaccines, the mortality among American troops was 0·2%, compared with 2·4% among Brazilians. An even more convincing example—this time of the naturally occurring disease—was reported from West Africa by FINDLAY.[11] FERNANDO and his colleagues[12,13] have given a further indication of the effect of nutrition in infective hepatitis and in the type of cirrhosis that may ensue. In Ceylon between 1945 and 1950 they studied 135 cases of hepatitis and 7 cases of cirrhosis, (5 with a clear history of hepatitis). The mortality among the hepatitis cases was 18·5%—i.e., almost one hundred times that in civilian epidemics in this country or the United States. The dietary history was available in 97 cases, and was classified into four groups for correlation with the mortality. Even the best diet, designated as A, was deficient in milk and eggs; the staple food was rice or flour, but vegetables and some animal food, such as fish or meat, were consumed daily. Diet B was similar, but animal protein was eaten only about twice a week. In diet C no animal protein was included; while diet D was very poor, consisting of rice or flour, some yams, and one vegetable, with meat or fish only once or twice a month. The depths in these different

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1. *Lancet*, Jan. 5, 1952, p. 33.
2. Mallory, F. B. *Bull. Johns Hopk. Hosp.* 1911, 22, 69.
3. Györgi, P., Goldblatt, H. *J. exp. Med.* 1939, 70, 185.
4. Daft, F. S., Sebrell, W. H., Lillie, R. D. *Proc. Soc. exp. Biol., N.Y.* 1942, 50, 1.
5. Himsworth, H. P., Glynn, L. E. *Lancet*, 1944, i, 457.
6. Trowell, H. C., Muwazi, E. M. K. *Arch. Dis. Childh.* 1945, 20, 110.
7. Waterlow, J. C. *Spec. Rep. Ser. med. Res. Coun., Lond.* no. 263. H. M. Stationery Office, 1948.
8. Gillman, J., Gillman, T. *J. Amer. med. Ass.* 1945, 129, 12.
9. Dible, J. H. *Brit. med. J.* 1951, i, 833.
10. Koszalka, M. F., Lindert, M. F. C., Snodgrass, H. M., Letner, H. B. *Arch. intern. Med.* 1949, 84, 782.
11. Findlay, G. M. *Mon. Bull. Min. Hlth, P.H.L.S.* 1948, 7, 11, 32.
12. Fernando, P. B., Mendoza, O. R., Rajasuriya, P. K. *Lancet*, 1948, ii, 205.
13. Fernando, P. B., Thanabalasunderam, R. S. *Quart. J. Med.* 1951, 20, 403.

groups were 5 out of 78 in group A, 4 out of 19 in group B, and 3 out of 12 in groups C and D combined. The incidence of complications is equally revealing: 8% in group A, 40% in group B, and 55% in groups C and D. Fernando and his associates also draw attention to the adverse prognosis in cases showing on admission to hospital anæmia and hypoproteinæmia—disturbances which they attribute to malnutrition, since they were present too early in the disease to have been caused by it.

Of the 7 cases first seen with cirrhosis, 5 had a clear history of infective hepatitis three to twelve months before. Of 2 other patients neither had a definite history of hepatitis and both had subsisted upon an extremely inadequate diet for seven months and for one year before the appearance of symptoms referable to the liver. Fernando et al. conclude that these two cases are examples of massive necrosis due primarily to nutritional deficiency and not secondary to infective hepatitis. Such cases, though extremely rare, are of great interest, firstly because they are the counterpart in man of the experimental disease, and secondly because they indicate an extremely low level of nutrition in the community and may be taken as a warning that the mortality from an outbreak of infective hepatitis would be exceptionally high. The work of Fernando and his colleagues also shows that a high proportion of the cirrhosis in such a community is a sequel to massive necrosis complicating a previous attack of infective hepatitis. The diffuse fibrosis of Laennec, on the other hand, at least in Ceylon, is not thus related to infective hepatitis.

Electrolyte Disturbances after Ureteric Transplantation

Bilateral transplantation of the ureters into the colon, first performed by Thomas Smith in 1878, remained a hazardous procedure until the brilliant experimental work of Coffey in 1909 made possible its development into what Crowell[1] described 25 years later as "the greatest humanitarian operation on the genito-urinary tract that has ever been proposed and successfully performed." Many variations of Coffey's original procedure have since been designed and adopted, and the continual appearance of new techniques suggests that the ideal has not yet been reached. The chief indications for the operation[2] are intractable cystitis (usually tuberculous) with contracture of the bladder; carcinoma of the bladder; vesicovaginal fistula, usually from obstetric trauma; and congenital malformations of the bladder and urethra, especially ectopia vesicæ.

Apart from the operative mortality, which in the best centres has gradually decreased to less than 4%, the chief dangers were thought to be ascending infection of the transplanted ureters, dilatation of the renal tract, and chronic pyelonephritis. In recent years, however, increasing attention has been paid to the profound electrolyte disturbances that may follow bilateral transplantation. It is surprising that this aspect was not investigated earlier, for the careful experimental work of Goldschmidt and Dayton[3] in 1919 showed that the colon readily absorbs chlorides, and rectal saline therapy is a long-established procedure. Apart from an isolated observation by Boyd[4] who reported chronic acidosis with rickets after bilateral transplantation of the ureters in a boy aged 7 years, nothing seems to have been written on this subject until 1950, when Ferris and Odel[5] reported from the Mayo Clinic that of 141 patients in whom bilateral transplantation had been performed 79% showed hyperchloræmia and 80% acidosis. Many of these patients were quite well despite the altered blood chemistry, but some had a characteristic clinical syndrome consisting in loss of weight, fatigue, excessive thirst, and a salty taste in the mouth. The Mayo Clinic workers attribute the hyperchloræmia to excessive absorption of chloride ion from the colon. The raised plasma-chloride concentration occurs without a corresponding rise in plasma-sodium; this relative sodium deficiency leads to a decrease in plasma-bicarbonate, and acidosis develops. A more intensive study of 1 patient, who also had a temporary nephrostomy, showed that the kidneys were still excreting a normal amount of sodium chloride. Odel et al.[6] suggest that the electrolyte disorder can be controlled by restricting intake of sodium chloride and administering sodium bicarbonate. They also advise that patients do not attempt to hold urine in the rectum any longer than is necessary.

Last year Lapides[7] found that colonic reabsorption is by no means the whole cause of the electrolyte disturbance. Of 22 patients who had had the operation 16 had some abnormality of the electrolyte pattern in the blood. Of these 16, every one had an abnormal pyelogram at some time after operation, and all had symptoms suggesting recurrent attacks of pyelitis. Lapides concluded that the electrolyte disturbances were due mainly to impaired renal tubular function resulting from repeated attacks of pyelitis. To prove this he did an ingenious test on 6 very coöperative patients, of whom 3 had normal and 3 impaired renal function. He instilled the bladder urine, obtained by catheter, into the rectum by continuous drip, and he found that the 3 with normal renal function had no electrolyte disturbance during or after the instillation, whereas the 3 with impaired renal function developed electrolyte disturbance similar to that after ureteric transplantation. Doroshow[8] suggests that the acidosis may be brought about, not only by reabsorption and low-grade renal tubular damage, but also by loss of base from the bowel through diarrhœa.

Whatever the mechanism, treatment with a salt-restricted diet and alkalis by mouth seems to give satisfactory results. The acute phase of acidosis can be combated by the introduction of a tube into the rectum, in order to promote rapid elimination of urine, together with appropriate intravenous therapy. Colonic lavage with plain water has also been used, in order to encourage diffusion of chloride from the blood into the colon. The ability to retain urine in the rectum for long periods, formerly a matter for congratulation, must now be sternly discouraged, and

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1. Crowell, A. J. *History of Urology.* Baltimore, 1933; p. 321.
2. Jacobs, A. *Proc. R. Soc. Med.* 1951, 45, 33.
3. Goldschmidt, S., Dayton, A. B. *Amer. J. Physiol.* 1919, 48, 419.
4. Boyd, J. D. *Amer. J. Dis. Child.* 1931, 42, 366.
5. Ferris, D. O., Odel, H. M. *J. Amer. med. Ass.* 1950, 142, 631.
6. Odel, H. M., Ferris, D. O., Priestley, J. T. *J. Urol.* 1951, 65, 1013.
7. Lapides, J. *Surg. Gynec. Obstet.* 1951, 93, 691.
8. Doroshow, H. S. *J. Urol.* 1951, 65, 531.

the patient should be instructed to empty his rectum as often as possible. Colonic reabsorption may perhaps be controlled by oral administration of calcium lactate; for, as GOLDSCHMIDT and DAYTON have shown, this inhibits the absorption of chlorides from the colon. Again, excessive chlorides might be removed by a suitable resin exchange material. Measures such as these may relieve the patient of the unpleasant necessity to empty his bowel every two or three hours.

Ureteric transplantation is never undertaken lightly. These additional hazards that have come to light will not diminish the indications for the operation, but should stimulate further research directed towards improving techniques and eliminating the complex problems arising from the presence of urine in the colon.

Annotations

SUCCESS AGAINST THE TUBERCLE BACILLUS

TIME has a way of dealing unkindly with early reports on new remedies; but three substances now being tested against various forms of tuberculosis in the U.S.A. seem to bear the hallmarks of great promise. These compounds, derived from an isomer of nicotinic acid, were produced independently by the Roche organisation and by E. R. Squibb & Sons. According to the *New York Times*,[1] one is isonicotinyl hydrazine ('Rimifon' Roche, 'Nydrazid' Squibb); the second is 1-isonicotinyl-2-isopropyl hydrazine ('Marsilid' Roche); the third is a glucosyl derivative of the first. The first of these three has so far proved the most effective.

At Seaview Hospital, Staten Island, New York, 190 patients have been treated with these compounds during the past eight months. All had previously failed to respond to other methods, including administration of streptomycin and *p*-aminosalicylic acid and surgical treatment. One physician said that the disease was stopped "right in its tracks." In all the pyrexial patients the temperature returned to normal in two to three weeks, and in a number of cases it dropped "precipitously." Within a week the patients developed "ravenous appetites," and some rapidly regained normal weight. At a conference in the offices of the National Tuberculosis Association, Dr. Geoffrey Rake, director of the Squibb Institute for Medical Research, said that isonicotinyl hydrazine appeared to be "many hundreds of times more effective than P.A.S., and significantly more effective than streptomycin." Experimentally, the effective dosage had been found to be substantially lower than that causing toxic effects. According to Hoffmann La Roche, these substances are beneficial not only in pulmonary tuberculosis but in other forms, including tuberculosis of bones and tuberculous meningitis. They are given by mouth; and they can be readily manufactured at, it is believed, low cost. They seem to be bactericidal rather than bacteriostatic; and so far no evidence of resistance has been detected.

However effective these drugs may eventually prove, they will not quickly solve the tuberculosis problem. As Dr. James E. Perkins, managing director of the National Tuberculosis Association, remarked, patients "still must rest and get other treatment, and people with unknown cases of tuberculosis still must be discovered to start treatment." Nor can these drugs repair structural damage caused by tuberculosis. In the words of Dr. Gordon Meade,[2] medical director of the Trudeau Sanatorium, Saranac Lake, New York: "There is no indication so far in our studies that these drugs will eliminate the need for careful medical supervision, bed rest, surgery, and other proven methods of treatment." Yet such sensible cautionary words need *not* dash the hope that this American work will take us a further stage in the attack on tuberculosis.

In this country isonicotinyl hydrazine (rimifon) is under trial by Roche Products Ltd, who inform us that it will be made available for general use as soon as possible.

SERVING DOCTORS AND THE PROTECTION SOCIETIES

NO communication is so persuasive as one that encourages discontinuance of an annual subscription. The War Office has issued to officers of the R.A.M.C. and R.A.D.C. a memorandum announcing that there is no need for them to belong to a medical or dental protection society "in connection with any treatment, &c., given in the course of their military duties." If they are sued as a result of professional services given while performing such duties, all they need do is to sign a form of retainer appointing the Treasury Solicitor to act for them:

> "The cost of any resultant settlement of the claim would then be met from the Army funds and no financial liability in connection with the settlement of the claim would fall upon the medical or dental officer concerned."

No doubt this is true. But is the official security really so complete as the protection which *it* proposes to supersede? Dr. Robert Forbes, as secretary of the Medical Defence Union, has written to the Secretary of State for War a letter describing the memorandum's advice as incomplete and misleading; and in our view Dr. Forbes is right in urging that Service doctors should not neglect the kind of protection obtainable by every member of the profession through the defence societies.

The Treasury Solicitor is the supremely competent head of one of the most expert and important of Government departments. He is the leader of the legal side of the Civil Service. His staff establishment is numerous, for the scope of his concerns is colossal. He is responsible for every legal problem in which the Treasury (which largely means the Government as a whole), the Army, and the Air Force are involved. He has branches which look after the Ministries of Transport, Food, and Fuel and Power. In addition to his divorce work as Queen's Proctor, he has a large Conveyancing Division, a Claims Commission Branch, a War Damage Commission and Central Land Board Branch, and a Prosecutions Branch. He has a finger in many a legal and administrative pie. He must decide which claims to fight and which to settle. But, with all his equipment, he certainly has not—he could not have—the specialised experience or the proved resources of successful team-work which are available to the medical defence societies. In the field, moreover, for which the War Office now offers his gratuitous services he will have a twofold responsibility. He will be representing primarily the Crown, the employing authority, and secondarily the officers whom the Crown (not always the most considerate of masters in the past) employs. If his two loyalties are in conflict, which of them is going to suffer? To lighten his heavy labours or to obtain the cheapest result he may (as Dr. Forbes points out) settle a claim out of court where the interests and reputation of the officer demand a fight. His department may think that officers have been negligent where a professional protection society would think otherwise.

Will the protection offered by the War Office be adequate cover? The defence societies can point out that the medical or dental officer may, through no fault of his own, be engaged in court-martial proceedings as accused, as prisoner's friend, or as medical witness. He nay need independent advice or representation in these nd in various other situations. Will the War Office rovide it? It is ungrateful to look a gift horse in the nouth, but it would be rash to abandon all examination f the animal's prospects merely because it comes out f the State stable and because the gamble is free.

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[1] *New York Times*, Feb. 22.
[2] *New York Herald Tribune*, Feb. 22.

TEMPORAL ARTERITIS

MOST of the recent papers on temporal (giant-cell) arteritis are written from the pathological standpoint; but their brief case-histories illustrate the wide variation in the clinical picture and emphasise the high incidence of blindness. In the case reported by Cardell and Hanley[1] the patient died from a brain-stem thrombosis two months after the first symptoms appeared; they found that 12 of the 27 fatal cases on record have died from cerebral vascular lesions. Clinically their case conformed to the recognised pattern—a vague pyrexial illness with diffuse pains, followed in a few weeks by severe scalp pain and progressive visual failure. Necropsy revealed changes in the ophthalmic, coronary, and other arteries as well as the temporal.

There are two views on the significance of the lesions found in other vessels. Cardell and Hanley follow Harrison[2] and Cooke et al.[3] in looking on temporal arteritis as an independent disease, differing from other forms of arteritis in affecting the larger, more elastic, and more muscular arteries of elderly people; in producing necrotic rather than inflammatory lesions involving all the vascular coats, particularly the media, which is heavily infiltrated with round cells; and in showing the characteristic giant-cells in the region of the fragmented elastic tissue. The other school classes temporal arteritis with periarteritis nodosa, eosinophilic arteritis, Loeffler's syndrome, and the collagen diseases dermatomyositis and scleroderma. According to Pagel,[4] the basic changes in all these conditions are essentially similar, and they differ only in the frequency and distribution of the lesions. This second interpretation is widely accepted by pathologists. Howells and Friedmann[5] describe a case which began with a chronic suppurative upper respiratory infection. Biopsy of the antral mucosa revealed almost complete replacement of the lining by giant-cell granulomatous tissue. The clinical course was rapidly downhill, and at necropsy widespread necrotising vascular lesions were found resembling those of polyarteritis nodosa. The vascular lesions may have been secondary to the severe sinusitis—an exaggerated tissue response induced by hypersensitivity to bacteria—or there may have been a hypersensitivity to some foreign protein or to the chemotherapeutic drugs used. This is no new theory, for the sulphonamides have long been suspected to cause polyarteritis nodosa, and the hyperergic antigen-antibody reaction has been used experimentally to reproduce the arterial lesions.

It is tempting to compare these pathological changes with those in rheumatic fever or the rheumatoid diseases. The relation of streptococcal sore throats to the onset of rheumatic fever is generally recognised: yet clinically the antibiotics do not affect the course of acute rheumatism. The presence of the streptococci in the tonsillar area apparently leaves some change which may be followed by rheumatic fever. Typical rheumatoid arthritis is quite distinct from typical rheumatic fever, but between these extremes there are many cases which do not belong with certainty to either group. It is significant, then, that some writers lay stress on the similarities between the Aschoff node of rheumatic fever and the histological findings in the less acute cases of polyarteritis nodosa, but say little about their difference. One must accept that there is a fair-sized family of conditions producing lesions in the small arteries or even capillaries, in which the process seems to start with an increase in permeability of the vascular wall, followed by deposition of fibrinogen, infiltration with lymphocytes or eosinophils in varying proportions, and destruction of the normal architecture of the vascular wall. The giant-cells which some consider so specific that they call the disease "giant-cell arteritis," are viewed by others as merely a cell response to the fragmentation of the internal elastic coat. Treatment is still unsatisfactory, though excision of a portion of the temporal artery, if the pain can definitely be localised to that area of the forehead, relieves the worst symptom. Boquien and his colleagues[6] gave antibiotics a further trial in their case, where fever with rigors was a prominent feature. Blood-culture yielded a gram-positive coccus which was relatively insensitive to penicillin: nevertheless, this drug was tried in large doses and had no effect. When aureomycin was given instead, there was definite clinical improvement, the rigors ceasing and the temperature falling to normal. In other cases blood-culture has yielded negative or inconclusive results, but this report will probably stimulate further investigations from the bacteriological aspects. On the whole, this line of approach does not seem promising. If temporal arteritis, polyarteritis nodosa, and the rest are all examples of an abnormal vascular response to some common stimulus, then the various clinical forms of acute and chronic arteritis may simply reflect the variations in resistance of the host's tissues. Young[7] tells us that "Cortisone does not, in general, influence directly a toxin or a noxious stimulus, but depresses the reaction of the cells of the body to the stimulus." More information on these diseases may come from clinical researches with cortisone.

ACCIDENTS IN FACTORIES

THE needs of the export market and the rearmament programme are extending British industry to the full. Each new machine which begins to turn in the factory or workshop and every new manufacturing process brought into use call for increased vigilance and protection against accident. The importance of this responsibility is emphasised by the bulky report which the Chief Inspector of Factories, Mr. G. P. Barnett, has signed for 1950.[8] The burden has fallen on his department at a time of staff shortage, and the inspection of factories has been of necessity less frequent than usual. Some relief might be gained, the report suggests, if a policy of self-inspection was more widely adopted by experienced employers in the larger concerns. Nevertheless the figures for 1950 show that our factories were, in general, safer places in which to work than they were in 1949.

At the end of 1950 there were nearly a quarter of a million factories in Great Britain, and more machinery was at work in them than ever before. The number without mechanical power of any kind was less than half the corresponding figure for 1940. Despite the abundance of complicated machines and an increase of 200,000 in the number of workers in the manufacturing industries, the accident total remained practically the same. The accident-rate per 1000 employed persons continued the steady decline which started in 1943. But the 799 lives lost and many thousands of disabling injuries give good reason for intensifying the safety campaign.

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[1] Cardell, B. S., Hanley, T. *J. Path. Bact.* 1951, 63, 587.
[2] Harrison, C. V. *J. clin. Path.* 1948, 1, 197.
[3] Cooke, W. T., Cloake, P. C. P., Govan, A. D. T., Colbeck, J. C. *Quart. J. Med.* 1946, 15, 47.
[4] Pagel, W. *J. clin. Path.* 1951, 4, 137.
[5] Howells, G. H., Friedmann, I. *Ibid*, 1950, 3, 220.
[6] Boquien, Y., Kernéis, J.-P., Hervouet, D., Moyon. *Pr. méd.* 1951, 59, 1774.
[7] Young, F. G. *Brit. med. J.* 1951, ii, 1535.
[8] Report of the Chief Inspector of Factories for the Year 1950. H.M. Stationery Office. Pp. 249. 6s. 6d.

Neglect or ignorance of the necessary precautions was all too evident in many accidents. For example, gloves were provided for workers in an ice-cream factory, but they did not wear them and got frostbite. This was a comparatively trivial affair, but some of the more grievous incidents make gruesome reading. Examples are given of badly designed machines which injured their operators, sometimes fatally and often seriously. The Chief Inspector remarks that designers are still giving insufficient thought to the elimination of danger points or to adequate protection where elimination is impracticable. One disturbing increase was in the number of people hurt while cleaning machinery in motion. Such accidents, says the report, indicate a serious lack of proper instruction and discipline. Eye injuries were still very common; while many were only slight, the aggregate of suffering and economic loss was tremendous. The rules laid down for those industrial processes which carry a particular risk to the eye have considerably reduced the danger, but neglect of the regulations continues to cause accidents.

The year saw no new hazards from industrial disease, but rather an intensification of the old ones. But Dr. E. R. A. Merewether, Senior Medical Inspector of Factories, and his colleagues in the Medical Inspectorate, have some good reasons for satisfaction. For the first time since lead poisoning became notifiable in 1895, a year passed without a fatal case; and poisoning by aniline reached a record low level. Anthrax was rather more frequent among those handling hides and skins, but no lives were lost. The control of many industrial diseases, as of accidents, has reached a stage where the standard of personal discipline of the worker makes all the difference between success and failure.

The lesson of the report is the old one that many disasters could have been avoided with a little extra care by somebody somewhere, and it should be taught most carefully to all young apprentices so that they may learn from the start the best way to work in safety.

MAN AND HIS ANIMALS

THE peasant farmer depends on his animals to provide him with food for his family to eat, wool to keep them warm, and draught power for his plough and his cart. The industrial revolution has provided only partial substitutes for farm animals, and human welfare is still intimately linked with their welfare.

Phillips,[1] reviewing the world's livestock in relation to human needs, finds that the average supply of animal protein in the daily diets of peoples of different countries varies from 4·7 g. per person in Indonesia to 86·3 g. in Iceland. Of 58 countries for which figures are available, only 18 have a supply capable of giving 30 g. per day per person—a level often given by physiologists as desirable. Thanks to our increased milk production, Great Britain with 45·2 g. is well up on this list. We also use just over 2·5 kg. of wool per person each year for clothing. With the development of synthetic textiles the proportion of woollen textile has fallen slightly. In 1920 throughout the world the material used for clothes was in the following proportions: cotton 85·5%, clean wool 13·6%, silk 0·6%, rayon 0·3%. In 1948 the figures were: cotton 75·1%, clean wool 11·3%, silk 0·2%, rayon 13·4%. There are still large areas of the world with a cold season where the people are woefully short of wool. Despite the rapid increase in the production of farm tractors, over 85% of total draught power on farms throughout the world is provided by animals. The U.S.A., Canada, and the United Kingdom are the only large areas in which the tractor power is greater than the livestock power. In not a few areas man himself is still the chief alternative to the draught animal in providing motive power for farm work. These few figures bring home the dependence of man on his animals.

Phillips outlines the possibilities for improving the quality of livestock. In many countries, and notably India, the number would be more than enough if only the efficiency of each beast was not so deplorably low. The sciences of genetics and nutrition, the control of infectious diseases, and chemotherapy can each contribute to improved health and efficiency of livestock. In many countries the time is ripe for a revolution in animal husbandry, and much of the necessary basic knowledge of animal physiology has already been gained. If man can learn to care and provide for his animals more effectively, he will get more food to eat, warmer clothes to wear, and more leisure from his labours.

CANCER-DETECTION CENTRES

WHILST perhaps admirable in theory, the periodic examination of symptom-free people in the hope of detecting incipient malignant disease has met with difficulties. Probably the most serious of these is the relative crudeness of most methods of diagnosing asymptomatic disease. Next, perhaps, comes the relatively elaborate examination that is necessary, and its high cost—not least in skilled personnel. Some say, too, that emphasis on preventive examination may make the public morbidly cancer-conscious, with a consequent increase in anxiety symptoms. Answers to these problems are gradually being formulated from the experiences of over 200 cancer-detection clinics in the U.S.A.[1 2]

One important conclusion is that unless the patients can be fully diagnosed at the clinic itself the proportion of failures will be large; for if patients are referred by the clinic to their own doctor with recommendations for further diagnostic procedures, about half of them will never have these procedures carried out. This implies that the detection centre must itself undertake all necessary investigations—even the most elaborate—so that ideally it should have the resources of a large hospital. Already, indeed, some hospitals are beginning to apply themselves to this work. Thus in certain hospital clinics in Sweden any outpatient attending for diagnosis is subjected to sigmoidoscopy. In other hospitals all patients have their chests radiographed and the erythrocyte-sedimentation rate measured. Such procedures, even if limited to patients over 40 years of age, must be costly in time, effort, and money. The expenses of separate cancer-detection centres will be even higher. At one such centre Koplin[1] found that the average cost per case of cancer discovered was just under $1000; but at other centres analyses have set the cost at $7000-8000.

The number of unsuspected cancers likely to be detected is usually well under 1%. It is noteworthy that Clifton and Rush[2] found that the ratio of cancers was no different in patients with and without symptoms. These workers, for what seem good reasons, feel that the clinic should not be restricted to people who have no symptoms. Of 12 cases detected 10 were treated at once, and the patients were alive and well at the time of the report; and of 977 patients subsequently followed up, only 1 was presumed to have had cancer that was not detected at the time of examination. The best procedure is still uncertain. At the New Haven Centre, described by Clifton and Rush, routine examination consists in a complete history and physical examination, complete blood-count, urine analysis, guaiac test of the stool, radiograph of the chest, smears of the cervix, and such additional investigations as may be indicated, including endoscopic examination and biopsy. Nevertheless, however thorough the tests, it is still rarely possible to recognise asymptomatic cancer in inaccessible situations

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1. Phillips, R. W. *Nutr. Abstr. Rev.* 1951, 21, 241.

1. Koplin, A. N. *Publ. Hlth Rep., Wash.* 1951, 66, 1339.
2. Clifton, E. E., Rush, B. *Surg. Gynec. Obstet.* 1951, 93, 719.

uch as the pancreas. Koplin, who agrees with this view, uggests that it would be wise to eliminate all routine rocedures (such as auscultation of the heart and blood-ressure determinations) except those that may help to letect accessible cancer. Such a saving of effort would, however, mean some loss of another function of these entres—namely, the finding of general defects in health. Koplin, for instance, in a group of 1987 women who were mostly Negresses, found hypertension (blood-pressure consistently above 140/90 mm. Hg) in nearly a quarter. Cervical lesions were found in 23%; and 32 had cancer of the cervix. In all, 2·1% of the whole group were found to have cancer, but only 1 neoplasm in an internal site was detected.

Plainly without improved diagnostic methods these centres cannot become fully effective. Equally plainly they do not represent the ultimate step against cancer; our eventual aim must be to detect and eradicate pre-cancerous states.

INFLUENZA VACCINES

It is now recognised that injection of the right vaccine at the right time will materially reduce the incidence of influenza. In a large trial carried out by the Commission on Influenza[1] in the U.S.A. in 1943, the incidence of influenza cases among 6263 vaccinated people was 2·2%, compared with 7·1% among 6211 controls. Figures of this order leave no doubt about the usefulness of vaccination. On the other hand, in similar trials carried out in the U.S.A.[2] and in this country[3] in 1947, vaccination was quite unsuccessful. The difference between the two trials was that the 1943 outbreak was caused by an influenza-A virus, which was serologically closely related to one of the components of the vaccine, whereas the 1947 outbreak was caused by A-prime viruses which appeared suddenly without warning and were not closely related serologically to the viruses used in the vaccine. The importance of using the right vaccine is again shown by a further study in the U.S.A.[4] The incidence of influenza during an outbreak caused by A-prime virus was three times greater in controls than in people vaccinated with a monovalent A-prime vaccine; and vaccines containing classical A and B viruses were without effect.

The right time is not easily gauged, since the usual vaccines give protection for only a few months. Salk and his co-workers[5] have found, however, that if the vaccine is mixed with oily adjuvants its potency is greatly increased and the serum-antibody levels remain raised for a long time. Nevertheless serum antibody cannot be equated directly with immunity, and it will be interesting to learn whether the new vaccines give longer protection.

Vaccination, though the best method we have of preventing influenza, is by no means the ideal. After vaccination a large amount of antibody appears in the serum while only traces are found in the nasal secretions[6]; and since infection with influenza virus is confined to the respiratory tract it seems likely that only the small amounts of antibody which actually reach this tract will be effective in limiting the infection. If some means could be found of increasing the local concentration of antibody in the respiratory tract, as has been done experimentally,[7] vaccination against influenza might become very much more efficient.

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1. Commission on Influenza. *J. Amer. med. Ass.* 1944, 124, 982.
2. Francis, T. jun., Salk, J. E., Quilligan, J. J. jun. *Amer. J. publ. Hlth*, 1947, 37, 1013.
3. Mellanby, H., Andrewes, C. H., Dudgeon, J. Mackay, D. G. *Lancet*, 1948, i, 978.
4. Meiklejohn, G., Weiss, D. L., Shragg, R. I., Lennette, E. H. *Amer. J. Hyg.* 1952, 55, 1.
5. Salk, J. E., Laurent, A. M., Bailey, M. L. *Amer. J. publ. Hlth*, 1951, 41, 669.
6. Francis, T. jun., Pearson, H. E., Sullivan, E. R., Brown, P.M. *Amer. J. Hyg.* 1943, 37, 294.
7. Fazekas de St. Groth, S. *Lancet*, 1950, i, 1101.

FINANCING THE UNIVERSITIES

Reporting on the five-year period 1947–51, the University Grants Committee give an interesting account of the use which the universities have made of the "unprecedentedly large sums which Parliament has provided," and presents the background against which the grant for the next quinquennium has been settled. The Chancellor of the Exchequer announced last week that the allocation, which in the present year is £16½ million, will be £20 million in 1952–53, and will rise to £25 million by 1956–57.

An increase of student numbers by 70% and the completion of £17 million worth of new buildings is no mean material feat. The committee are satisfied with the quality of this greatly increased number of students: they find that, although there has been only a small increase in the number of the outstandingly able, the really weak student finds it difficult to gain entry. There are far more applicants for the places in medical schools, which are not much more numerous than they were; but, although the committee find "some evidence of a general improvement in quality" the vast choice at the schools' disposal does not seem to enable them to select a student body with a better examinations performance than that of the bad old days when almost anyone could become a medical student. Qualifying examinations are not competitive: and one might expect that the present-day student, chosen from so large a band, would pass final examinations at the first attempt. The fact that the proportion passed is much the same as it was before the war suggests several disturbing explanations: assuming that the examinations are similar, are we to suppose that the teaching is not so good or that the method of selection is somehow wrong?

The recurrent grants for medical education rose from £1·8 million in 1947–48 to £3·2 million in 1951–52. Besides meeting rising costs, this expenditure has provided 55 new full-time chairs in clinical subjects and has allowed reorganisation of the British Postgraduate Medical School in London into a Federation incorporating a wide range of specialties. Great though the increase of expenditure on medical education is, there are other university subjects in which the percentage increase has been even greater. The committee have also provided additional recurrent grants for science and technology, the subjects in science being mainly biological, and in technology mainly the various forms of engineering. There has been some question of the wisdom of large increases in technological training by universities, on the grounds that the university graduate well educated in the humanities is highly adaptable and is likely to be of the most use to the community in the long run: but it certainly seems desirable to provide the technological student with a university atmosphere if possible; and it is wise to train large numbers of men in subjects which will give them an outlet, rather than repeat the mistake of the German universities, which turned out hordes of graduates for whom there was no acceptable employment, leaving them to swell the ranks of the discontented—and the Nazis.

In general, the policy of the University Grants Committee has been obviously sound, and has well merited the confidence which Parliament has shown, and still shows, in so liberally supporting university education.

The Index and title-page to Vol. II, 1951, which was completed with The Lancet of Dec. 29, is now in preparation. A copy will be sent gratis to subscribers on receipt of a postcard addressed to the Manager of The Lancet, 7, Adam Street, Adelphi, W.C.2. Subscribers who have not already indicated their desire to receive indexes regularly as published should do so now.

Special Articles

UNINTENTIONAL CONFOUNDING IN MEDICAL RESEARCH

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WHEN two factors are always associated in a survey or an experiment, it is impossible to decide whether any results produced by them are due to one or the other or both. In such a case the two factors are said to be confounded. As an example of unintentional confounding, take this statement by Williams (1905):

> "*It seems to be proved*, however, that the average weight of children whose mothers have worked throughout pregnancy is lower than that of mothers who are able to rest even only for a few weeks before the birth of the child."

This observation, especially in the guarded form in which it was made, may well have been correct as a simple statement of fact in 1905; but if the writer intended to imply that a working woman who rested from work for a few weeks before childbirth would, on the average, by that fact alone, ensure that her baby would be heavier than it would otherwise be, then scepticism seems justified. There would obviously be many relevant differences between those pregnant women who remained in employment until the time of childbirth and those who either did not have a job or were able to give it up during pregnancy. In other words, the effect of rest was very likely to be confounded with several other factors.

It is easy to recall many further examples in medicine, where the conventional answers must be interpreted with due regard to the danger of unintentional confounding. Can we say whether death-rates for particular diseases are lower for patients treated at home than for those treated in hospital, or whether breast-feeding is superior, in some defined aspect, to artificial feeding? A less urgent and more subtle difficulty lies in the statement that married people live longer than single people—a statement which can perhaps be analysed more easily if we reflect on a similar assertion that professors live longer than medical students. In each of these cases the main factor about which we seek information is entangled with various others which are trivial in their intrinsic interest, but which may nevertheless have an important effect on the results. Sometimes there may be practical reasons why it is impossible to isolate a factor from various confounding effects, and the problem, in the form in which it first attracts our attention, may then be insoluble. I do not know how you would find out, for example, whether marriage is likely to lengthen the life of human beings, though a similar sort of question could be settled experimentally in the case of the rat, let us say, if it were thought interesting and relevant to do so.

In discussing these problems some care is needed to skirt difficulties that are merely verbal. Suppose it is asserted that there is a lower maternal mortality among mothers who have their babies at home than among those delivered in hospital. One would have to accept this conclusion as a fact if it were the result of a suitable survey in a particular community. But what does it mean, and how can the information be used? It certainly does not mean that a pregnant woman could improve her prospects of a safe childbirth by deciding to have her baby at home rather than in hospital; though it would sometimes be interpreted as giving just this interesting information. To accept such an interpretation is to go beyond the simple findings of the survey and to embrace a particular explanation of them—namely, that the relevant difference between the two groups of mothers is in the place of confinement. But this factor may well be confounded with so many others, too obvious to require detailed discussion, that one is entitled to remain unconvinced by the argument. The safe conclusion from the original survey therefore amounts to little more than the indication that there is some difference between the two groups of cases, and that the difference calls for further analysis; but it may turn out that the cause is trivial from the point of view of someone trying to improve obstetric practice. It might be, for example, that the hospitals had a relatively high proportion of patients who were expected to have a complicated labour.

SURVEY VERSUS EXPERIMENT

It is obvious that there is a greater chance of undesired confounding when information is being sought through observation rather than experiment. In fact this touches on the essential difference between these two methods of investigation, and provides the reason why, in general, results obtained by observation are not regarded as final when it is possible to test the relevant hypothesis by experiment. This difference remains even when the observations take the form of a planned survey, in which some extraneous factors can be isolated, and thereby eliminated. Surveys are probably used more in medical research now than they were in the past. They have their place, especially in description or estimation—e.g., to determine how much milk per head per day is consumed by young children; or the length of the gestation period in a particular group of women; or the incidence of rickets in England. But when it comes to the question of testing hypotheses—e.g., that the consumption of an average of 1 pint of milk per day enables children to maintain a greater growth-rate than the consumption of $^{3}/_{4}$ pint; or that the length of the gestation period is influenced by the quality of the diet; or that the consumption of meat has a protective effect against rickets—then the method of the survey may lead to difficulties with confounding. This is not to deny that valuable information about hypotheses can be obtained by surveys, or to claim that all important confounding is avoided by experiment; but it is usually possible to put the hypothesis under greater strain, as it were, by experimental methods, and the thoroughness with which a theory is tested is very important. As soon as a hypothesis has won provisional acceptance, progress is more likely to come from those who plan their research as if to overthrow it than from those who simply seek extra facts that are likely to support it. Those who attack a theory are most likely to find its weaknesses; and if it is well founded, this fact can be revealed more convincingly by the failure of critics than by the endorsement of friends. The drawback of the technique of the survey is that unavoidable confounding often makes it possible to give several plausible explanations for a single set of findings; and the method, therefore, so far as the testing of hypotheses is concerned, lends itself more to providing general support for a theory than to subjecting it to acute criticism.

An illustration is provided by a comprehensive survey of [illegible] children, which is being carried out in [illegible] by Hutton et al. (1951). From 1945 onwards sodium fluoride has been added to the drinking-water of this city and the incidence of dental caries has greatly decreased as compared with a base-line figure established in 1944. This information is undoubtedly of value to the public-health service; but it is worth pointing out that the project will not supply much additional evidence about the hypothesis that dental caries can be reduced by bringing the fluoride-content of the drinking-water up to some prearranged level. The incidence of caries amongst children in London and in Norway declined considerably in the 1940s, so that the possibility of confounding factors cannot be ignored. It is true that the hypothesis is also strongly supported,

satisfactory hypothesis untenable beyond any shadow of doubt; a theory is more usually destroyed by a systematic undermining of its foundations.

AVOIDING THE DANGER OF CONFOUNDING

The danger of unintentional confounding is ever present and it would be reasonable to expect that experimenters, either implicitly or explicitly, should have developed techniques that avoid some of its pitfalls. And so they have. Sometimes they have made a deliberate attempt to pair experimental and control subjects so that certain important factors which might affect the outcome of treatment are equally distributed in the two groups, and not associated with the treatment alone. They may use sham operations to distinguish the effects of any operation from those of a specific one; or give saline injections to separate the effects of the drug from those of the vehicle. One of the most successful methods has been to lead up to a theory by several different paths; it is unlikely that a confounding factor would crop up in a number of separate situations. The argument has an element of hope as well as of reason, but it often works out well. One of the best illustrations is the work of Harvey on the circulation of blood, where he drew on a variety of experimental evidence to support his thesis. Again, the evidence which located the pace-maker of the heart came partly from embryological studies, partly from comparative anatomy and physiology, and partly from electrophysiology. A final example is the array of evidence gathered by J. S. Haldane to show that so-called vagus apnœa following hyperventilation is produced by the lowering of the tension of carbon dioxide in the blood rather than by stimulation of the vagus. The great experimenters of medicine have used this method freely and convincingly, but it is only valid if the different experiments used are independent of one another, and not merely ingenious repetitions of the same central, and possibly false, argument. Many theories, supported by arguments running from (a) to (f) or further, have eventually been overthrown because this point was neglected.

The great contribution of the statistician to the solution of unintentional confounding has been to emphasise the importance of random grouping in the experimental method. If the population from whom the subjects of the experiment are drawn contains some individuals with an unknown characteristic that will have an important effect on the outcome of the experiment, then random grouping ensures a fair chance of their equal distribution. These individuals may be a nuisance because they enlarge the error of the experiment, but the important thing is that they should not bias the results; and random grouping gives efficient, though, of course, incomplete, protection against bias. Sometimes a recognisable characteristic of the subjects of the experiment is known to affect the response being measured and is therefore likely to produce partial confounding. This factor may be qualitative; for example, the sex of an animal may affect its gain in weight during a nutritional experiment. The statistical procedure in such a case is to modify random grouping, to give equal numbers of each sex in the various groups; but such grouping is still essential within the limits of this restriction. In other cases the potentially confounded factor may be quantitative; for example, the initial weight of an animal may affect the response in the same experiment. In this case a record is taken of the initial weights, and the analysis of covariance enables a correction to be made to compensate for differences in these weights between the various groups.

An industrious critic can always find elements of confounding in even the most carefully designed experiment. In this respect confounding is like bias; we should attempt to abolish it as far as practicable, and then come to terms with what remains. The success of the bargain we strike will depend largely on our background knowledge of the problem concerned. And success, however welcome, is only provisional: the process of discovering and eliminating confounding factors must continue as long as progress is made.

REFERENCES

Harington, C. R. (1933) The Thyroid Gland: Its Chemistry and Physiology. London.

Hutton, W. L., Linscott, B. W., Williams, D. B. (1951) *Canad. J publ. Hlth*, 42, 81.

Murray, M. M., Ryle, J. A., Simpson, B. W., Wilson, D. C. (1948) Medical Research Council memorandum no. 18. H.M. Stationery Office, London.

Williams, D. (1905) *Brit. med. J.* ii, 929.

Personal Papers

THE GENTLE ART OF LOCAL GOVERNMENT

BY A FORMER EXPONENT

TODAY all over the world new forms of government are being tried. In our own fairly venerable constitution the tendency may be towards centralisation of power; but in many politically immature countries, who are only now feeling their way towards self-government, the first step must be the delegation of power from a paternal central authority to independent and inexperienced provincial assemblies.

The evolution of groups of people from simple tribal organisations to the complex set-up of government on modern democratic lines is a slow business, and if the new organisations are to work efficiently and smoothly, and not to degenerate into agencies for the satisfaction of the ambitions of individuals and sections, every step will have to be carefully guided.

COMMITTEE

One of the most widespread instruments of government is the committee. In embryo form this can be:

(a) *An autocracy* which puts forward, as a regular thing, fantastic and impossible projects, under the driving force of the most important, richest, or most belligerent of its members, sometimes with an eye to the main chance.

(b) *A democracy*, so democratic that the members' normal approach is excessively cautious and nothing is ever done. Their timidity, in face of public reactions to the bill, drives them from the firm ground of righteousness and strength to the thin ice of indecision and dithering. Through this ultimately they fall, and at the next municipal elections the less wily are drowned in the cold and thankless actions of their unappreciative constituents.

(c) *Something between the two*; and it is the lifelong job of the professional counsellors to steer between the rocks and shoals—a minor graze here and there is of no consequence—and to keep the ship of municipal state afloat on an endless sea of more or less stormy waters.

The ordinary reaction of a newly formed committee is to regard itself as a sort of rubber stamp for the chairman, to dance to his tune, and to accept his instructions without question. On his part, he is content to look on himself as a little dictator and the committee as a flock of sheep, or herd of goats, necessary for the sustenance of his own projects. If, as is usual, he is chosen—or chooses himself—because he is the most important, or has the other characteristics mentioned above, his path is made easier by his members' reluctance to face up to him either within the council chamber or when he corners them outside.

The conception of the chairman as the voice of the committee has little appeal to debutants in this business, and the practice of circulating the chairmanship, so that all members have a turn, is not favoured by the more powerful elements. A man who holds a chief's position is not likely to submit to the opinions of a person or a group whom he regards as his social inferiors or lesser lights in the hierarchy. Perhaps he may be taught to pay lip-service to this democratic principle, but when a row comes the veneer will crack and he will proclaim himself in no uncertain tones.

PROCEDURE

Another interesting observation, when democratic practices are introduced, is the variation in interpretation applied to rules of procedure. It is rare for more than one or two earnest members, and those usually with a legal twist, to study the rules at all. Most will accept any direction, provided it cramps the other fellow's style and leaves them free to speak their minds whether to the point or not. The ordinary technique of addressing all remarks to the chair only obtains when such remarks are formal and of no consequence. Anything which gets under the skin is aimed across the table, and the deliberations develop into a dog-fight with no more consciousness of rules of procedure, chairmen, and the dignity of bumbledom, than is shown in similar circumstances by that otherwise reasonable animal. In the end, however, some business is transacted, though most of the members leave the meeting not quite sure of what they have done or what has been done to them. The officials are usually satisfied if item one on the agenda—Payment of Salaries and Accounts, is passed. The rest can wait.

And now comes the turn of the secretary or clerk to the council. He has to prepare the minutes. Since new committees love to plunge into the mazes of "amendments" and "amendments to amendments," until the original resolution can only be disentangled from the mess with the greatest difficulty, it requires an intensity of attention and the nose of a champion to follow the trail. In the end, the clerk generally writes the minutes from what he thinks has happened; and, if he is an experienced clerk, that should be sufficient—until the next meeting. But it is not always so. For once the importance of minutes is understood—namely, that something said by a member may be used against him at a future date when he may have entirely new ideas on the subject—then members begin to worry and a visit to the clerk follows.

Another difficulty in handling inexperienced committees is to get them to decide about anything. All the members have ideas, and, if allowed, will argue them indefinitely, especially when major matters, such as bicycle allowances of junior employees, are being discussed. But where it is a question of policy involving the spending of sums of real money, they are like trapped creatures seeking a way of escape, and any loophole will do. Any slight lack of technical information, any excuse for fresh inquiry, or the absence of a member who is for the moment regarded as an authority on the subject, is used as a reason for postponement of resolution. Further, after a vote has been taken by show of hands, some cantankerous and determined fellow may insist on a record by voice of individual members, and it is remarkable how the original opinion of the committee can be swung by this manœuvre. Finally, we get a succession of *arrangements provisoires* (temporary accommodations), and a string of exceptions all of which are designed to blunt the edge of the axe of decision, which might otherwise land the severed head of responsibility into the collective committee lap.

CHECKS

There are two instruments which may curb committees and councils when their proposals skid about on the edge of strict legality. One is the practice of "surcharging," by the decision of Ministerial auditors, individual members when their actions result in the spending of public money for purposes not authorised by the laws and regulations which they are called upon to administer. This is a serious matter and has a deep effect on their morale. To have to endure in the public interest a kind of martyrdom—that it is self-imposed is neither here nor there—and then to have to pay for it is a bit thick.

The second brake on a committee is the nosy reporter of some disreputable national newspaper. This individual, after calculation, decides that the amount he can get to be squared is not equivalent to the value of the scoop he has gathered; and he writes it up, laying on the colour where it hurts most. His paper has no fear of action for libel, for it carries a heavy insurance policy for just such eventualities. So the tale as published loses nothing in the telling, and is received joyously.

The existence of D.N.N.s (disreputable national newspapers) is something which has constantly to be borne in mind by law-makers. Under the slogan of "defending the rights of the people," and with frequent use of the word "alleged" prefixed to any string of lies and calumnies, they hurl mud about in all directions on the assumption that much of it will stick and take a lot of cleaning off. Thus, they get a respectful attention which they do not deserve.

THE M.O.H.

Like the engineer and other heads of departments, the medical officer has to prepare the technical side of his committee's agenda, and he should not allow himself to be elbowed out of this by the town clerk, who officially compiles and issues the completed document. To save himself trouble, the M.O.H. should stick to a routine presentation of items, giving figures, percentages, and ratios, which will not be listened to, but which will be a useful record and may get him out of a jam in the future. He should not allow these statistics to be taken as read but should use them for filling in time. He should keep anything likely to raise awkward questions until nearly the end. Councillors, like anyone else, grow weary and feel the pangs of hunger, and if the M.O.H. has cultivated a reputation for being long-winded they will avoid getting him on his feet when they know that the point in question is not the last on the list. An M.O.H. from the Clyde has an advantage here. None but fellow Glaswegians can understand him, and the effort to translate into the common tongue the extraordinary sounds which he makes gains for him looks of alarm when he stands up and sighs of relief when he sits down, and a determination to avoid giving him any reason to repeat the dose. But from time to time, there occurs an awful manifestation of human perversity, the all night sitting. This is like the onset of a disease and attacks councillors en masse. It cannot be foreseen—there are no reliable prodromata—and it is insidious in its development, with hardening of the signs and symptoms as the evening progresses. Nothing can be done to break it. Hunger and thirst are resisted and there is a continuous restoration of energy from within, and an astonishing exhibition of endurance.

When the M.O.H. has to initiate anything he should remember that a subtle appeal to vanity will always bring results. He must never appear to have any originality of thought, nor expect to get any credit for what he may have done. His line is to insinuate into the mind of his chairman such plans as he has thought out for the betterment of his town or county. He will, in the course of talk, make it appear that these notions originated with the chairman himself—an easy process, as the obvious details which he will carefully omit will be promptly supplied by the other and the M.O.H. will foster the conviction *that the chairman thought of the whole thing first.* The chairman will approach the town clerk: "I have been thinking that it would be a good thing, in fact it is high time, that a drain should be built from A down such and such a street to B, to join the main sewer there." The clerk will be instantly on the alert, and, if he does not know already, he will discreetly inquire from his colleagues what personal or financial interest the chairman may have in properties along the course of the proposed drain. If the chairman is in the clear, the clerk will, "having looked into the matter" place the proposal on the agenda for the next health committee. The health committee will approve, because out of all its members there are sure to be some who will benefit one way or the other; and, if the price of real estate goes up as a result, the pity of it is that neither the town clerk, nor the engineer, nor the medical officer dare have a finger in the pie.

Another useful move is to drop a hint to the chairman of the finance committee. Thus another and most powerful ally may be secured. But there is always the risk that the finance man may be completely detached from reality, in which case the battle will be long and hard when his committee comes to examine the project.

However, a good case will go through sooner or later, *especially if there is a government grant hanging to it.* The chairman will reach the exalted rank of a public benefactor. The M.O.H. will have the satisfaction of achieving his purpose. There will be sundry disbursements by persons unknown to parties still more unknown. There will be employment for many. Property value along the drain will go up; the drain will go down. The contractor will get a fine profit. There will be a formal inauguration by the local M.P. with long speeches *and cheap champagne*—entered among "items, miscellaneous" as "extra cement"—and everybody will be happy.

AND YET

And yet, with all the humbug which clutters it up, this is *probably the most satisfactory and fair method* of self-government which has ever been devised. It is certainly the most honest, for the simple reason that everyone in it has a full opportunity to watch everyone else and crime does not pay.

So, cheers for the gallant cavalcade of Bumbledom as it makes its progress through the streets on Mayor's Sunday—His Worship in scarlet and fur and gold chain; the Clerk in wig and gown; the Aldermen in cocked hats and long robes and ribbons; the Councillors in ancient frock-coats and moth-eaten toppers; the wretched and down-trodden officials in a mixed grill of what they conceive to be formal dress; the police band with its battered brass; the fire-brigade; the boy scouts; a few obscene dogs; and finally one of the town's garbage carts which always seems at such times to bring up the rear. There *they* go, *bless 'em all, the* greatest show on earth; Britain, France, Belgium, Holland, all the same; and where would we be without them?

Parliament

Social Services and the Crisis

OPENING a debate on the economic situation in the *House of Lords* on Feb. 19 Lord PAKENHAM described the Government's attitude to the National Health Service as lamentable. Was it really supposed that exports would be increased, or imports diminished, by the proposed new charges? Nor did he think it was seriously argued that these measures would diminish abuses of the health service system. *The Government's* proposals, he declared, were a redistribution of income in favour of the healthy against the sick. Lord Pakenham said he regarded that as defeating the whole purpose of the National Health Service scheme. Viscount SWINTON, Chancellor of the Duchy of Lancaster, answered Lord Pakenham's *criticism by quoting Mr. Gaitskell's* words:

> "It is clear that it is not possible in existing circumstances to permit an over-all increase of expenditure on the Health Service. Any expansion in one part of the service must in future be met by economies, or, if necessary, by contraction, in others."

Surely, said Lord Swinton, that could be said with even greater force today.

Lord SILKIN said it had been argued that the proposed charges would reduce the call on dentures, surgical aids, hearing-aids, and so on. If so, it was a deterrent which he regarded as wrong in principle. It was wrong to prevent people getting medicine because they were unable to pay for it. If there was abuse the Government should deal with it in some other way than through the power of the purse. The people deterred might be the very people who in the opinion of the medical profession ought to get the medicines or appliances. Lord BALFOUR of BURLEIGH said that this country had achieved such a high standard of living that we could afford cuts if they were necessary to avoid collapse of the whole system.

Viscount WAVERLEY pointed out that *food subsidies* had not been conceived as a social service, indeed they were clumsy and inefficient. It would be worth while, in his view, to get rid of food subsidies even if the whole saving had to be redistributed for the benefit of the poorer sections of the community—who might suffer from their abolition. *The illusion of unlimited resources,* he believed, must be destroyed and it must be brought home to everybody that, however liberal the social services might be, a man still had a primary duty to maintain himself *and his family in addition to making his due* contribution to the common good. Unfortunately, so long as one of our main concerns must be to keep the cost of living down, there was nothing very heroic to be done, and we must be content with a modest beginning. He believed that the Minister of Health was perfectly right in claiming that the changes now to be introduced in the health services would help to eliminate abuses and promote efficiency and economy. To suggest that *the* foundations of the Welfare State were being undermined was a palpable absurdity. We should still possess *social* services second to none in the world.

Lord WOOLTON, in ending the debate, for the Government, appealed to the Opposition *not to make* the Welfare State a party matter. *It was something that* had grown up over many *generations.* Its friends were those who wanted to see it persist but wanted to see it built on a solid and enduring foundation.

QUESTION TIME

Reprieved Hospitals

Mr. FREDERICK WILLEY asked the Minister of Health what action he proposed to take to avoid the closing of five hospitals in the Newcastle region consequent upon the reduction made by him on the estimates of the Newcastle Regional Hospital Board.—Mr. H. F. C. CROOKSHANK replied: I understand that the funds to meet revenue expenditure in 1952–53 which I have now been able to allow the board will probably obviate the closing of any of these hospitals.

Hospital Food

Mr. N. N. DODDS asked the Minister if he was aware of the concern caused by the decision of the South-West Metropolitan Regional Board, controlling over 300 hospitals, to spend no more than 21s. a week on feeding each patient, at a time of rising prices, and if he would increase the amount; if he was aware of the action of the board in cutting to 14s. a week the maximum amount to be spent on food for each mental patient under its jurisdiction; and if he would ensure that no economy measures were made at the expense of the patients' diet.—Mr. CROOKSHANK replied: I am informed that the board have asked management committees, in preparing their estimates for the next financial year, to regard as maxima for their groups certain figures of expenditure on provisions based on averages in the region. In addition they have warned committees to take account of possible price rises in framing their estimates. This is an interim measure pending a further detailed investigation into the costs of provisions and, on the information at present available, I see no reason to intervene.

Conditions at a Military Hospital

Mr. F. A. Burden asked the Secretary of State for War if his attention had been drawn to the unsatisfactory conditions at the Connaught Military Hospital for tuberculous patients at Hindhead, Surrey.—Mr. Antony Head replied: The accommodation at this hospital is not all that I should wish. If, however, it were not used, tuberculous patients would have to wait for a bed in the limited general hospital accommodation elsewhere and would not have the advantage of early specialist treatment. Further improvements in the structure and amenities are in hand, and I am satisfied that recent allegations about the conditions were much exaggerated.

Old-age Pensioners' Prescriptions

In reply to a question Mr. Crookshank stated that the cost of exempting old-age pensioners in England and Wales from paying for N.H.S. prescriptions might be about £1½ million.

Surgical Foot-wear

Replying to a question Mr. Crookshank said he was aware that some surgical boots cost from £12 to £15 a pair, and that this charge was often beyond the means of the applicants. It was proposed to make a fixed charge of £3 a pair for surgical boots and shoes.

Sanatorium Waiting-lists

In answer to a question Mr. Crookshank said that the number of people in England and Wales waiting for admission to tuberculosis sanatoria at Dec. 31, 1951, was about 8200.

Care of Aged

Replying to a question Mr. Crookshank said there were at present 67 geriatric units established, many of which served several hospitals.

Dentures and Spectacles

Replying to a question Mr. Crookshank said that from the revised health service estimates it seemed probable that expenditure on the general dental services as a whole would be about equal to the estimate, while that on the supplementary ophthalmic services would be about £5 million below.

Replying to a similar question Mr. James Stuart, Secretary of State for Scotland, said that in Scotland the expenditure on the general dental service as a whole would probably be about equal to the revised estimate, while that on the supplementary ophthalmic service would be about £50,000 below.

Hearing-aids

Replying to a question Mr. Crookshank said that 110,215 applications for hearing-aids under the National Health Service in England and Wales were outstanding on Aug. 31 last. Out of that number something like 25,000 had since been supplied. In 1950–51 the cost of instruments—excluding batteries for electrical hearing-aids—was £327,000. The revised estimate for the current financial year was £545,000. The proposed charges were estimated to produce about £61,500 in a full year.

In answer to a similar question Mr. Stuart stated that in Scotland the number of applications for hearing-aids outstanding at Jan. 26 was 6653. He said that the cost of supplying hearing-aids under the National Health Service in Scotland in 1950–51, excluding the cost of batteries and of fitting, was £56,500. The estimated cost for the current financial year was £57,700. The estimated receipts from the proposed charges for hearing-aids for a full year were £17,000. It was not possible to estimate the cost to the Exchequer of any assistance given by the National Assistance Board to applicants for reimbursement of these charges.

". . . Take good care of the diabetes and the pregnancy will take care of itself."—Prof. M. A. Van Bouwdyk Bastiaanse and Dr. I. S. Sindram. *J. Obstet. Gynæc.* 1951, 58, 996.

In England Now

A Running Commentary by Peripatetic Correspondents

Hard frosts may be a blessing by checking insect pests and breaking up the soil for spring cultivation, but they certainly show up our smaller sins of omission. Our house had a new water system not long ago, and much time and money were spent on lagging it. But a house built about A.D. 1500 does not take kindly to the niceties of modern plumbing and what the builder calls "lagged ducts." That foot or two of pipe in an awkward corner behind a large beam caused all the trouble. Still, a whole street of modern houses in Kensington was frozen up recently, so age is not everything.

Most Englishmen look on thawing-out pipes as an annual mortification of the soul, with traditional rules to be observed. Blow-lamps and most other heaters are barred, because of the risk of fire, except in accessible places which never get frozen up anyway. Hot water and rags—if you can get any water to heat—work well; but the operation has to be conducted under a barrage of remarks from the distaff side about making a mess. For this reason some authorities favour rubber hot-water bottles, though they admit that the limited number of kettles available imposes a time factor which may spell failure; whereas the blow-lamp-and-bucket school justly claim that they can keep on indefinitely, if need be.

These household inconveniences seem rather trivial if next day you have to treat two bad fractures resulting from falls on slippery steps. People don't sprinkle sawdust or grit around their houses these days as they used to do. Sawdust is far the best of the antislip applications, but how many houses nowadays can collect enough to do good? Only the small proportion in country districts where mill-saws or sawing horses are important articles of domestic equipment for cutting up firewood. Sand is second best; but it leaves tell-tale marks on the carpets, unless the family's footwear toilet is of a much higher order than ours. Ashes—well, in an hour or two they disintegrate into a black paste, because (as our old Arthur puts it) they lack body. They also leave a stain that lasts well into the spring when, amid the bursting buds and general jollifications, nobody wants to be reminded of the winter.

* * *

In the Barnes Hall of the Royal Society of Medicine the bell-push which rings to the lantern operator has been ingeniously placed at the point on the lecturer's desk where his right elbow naturally presses if he leans upon the desk. I have been making a study of the reaction of different lecturers as they lean upon this push button. I should like to read a paper on this subject at the R.S.M., but as I am nervous of leaning on it myself I have decided to publish my results in this column.

First, there is the very nervous man. He starts off safely enough standing well behind the desk. The cruel thing is that the buzzer doesn't catch him till his first moment of confidence; then, when he is just warming up, he leans confidently forwards on the desk and immediately reverberating buzzing fills the entire hall. His talk falters and stops. He gazes round with a wild surmise, wondering if it is a firebell or whether it is a special alarm to show that he has spoken too long. He is far too nervous to realise he is ringing it himself. He leans there wretchedly, his elbow still on the bell and tries to speak through the noise. Various members of the audience try to signal to him that he is leaning on the bell-push, but in his nervous state he cannot comprehend them and begins vaguely to wonder what is wrong with him—Are his trousers coming down? Has he said something rude by mistake? At last, the secretary of the meeting leans sideways from his seat on the dais and tells him what he is doing: with a muttered apology he lifts his elbow and the buzzing noise stops. Then he starts again in dead silence, but he is a broken man, his confidence shattered, his flow of words less coherent; for the rest of the talk he eyes the bell-push like an unexploded bomb.

Then, the moderately nervous man. He reacts somewhat differently because, though nervous, he is sufficiently orientated to realise what has happened. As soon as the buzzer rings he shies like *a startled* horse and his elbow jerks off the button as if he had got an electric shock.

The dishonest man pretends he meant to ring the bell on purpose and firmly says "I rang the bell for the first slide please," even though he had no intention of showing it yet.

It is remarkable that the lantern operator, invisible in his wooden tower, can after years of experience always tell whether a push on the button is inadvertent or advertent so to speak, but he may be defeated by the dishonest lecturer.

The really confident extrovert deals with the buzzer in quite a different way. When the shattering noise first starts he beams at his audience and says "I believe I'm leaning on the buzzer," then he shouts across the room to the operator "I don't want a slide yet, I'm leaning on the buzzer." Then leisurely he lifts his elbow and resumes his talk. Men of such powerful calibre are rare, and few speakers can survive the ordeal by buzz without severe psychic trauma. Selye's work on the adaptation reaction shows what irreparable harm can be produced by alarm and stress. Eosinophil-counts before and after leaning on the bell-push might be revealing.

Maybe some responsible person will read this and move the bell to a safer position; but perhaps it would be a shame to remove this hazard which has for so many years entertained the audience during the less exciting lectures.

* * *

"Hullo, hullo! Yes, it's me all right. You want to know the best doctor to look at your brains? Why, Dr. Gargle, of course. He's better than any of them, without a shadder of a doubt, Mrs. Pinkle. (These telephones *is* getting bad, aren't they?) If you lets them run away with you, you never know where it will end, do you? (No, not the phones, dear; your brains.) My hadvice is—see a proper spechalist, every time. Talkin' to yesself is the first stage, my dear. Mark my woords. Look at old Hitler. That's how he began. And look how he ended. Have nothing to do with those homopathologists. They'll take out your hinside and as likely as not forget to put it all in again. My hoosband went to one o' them; I bought him a new tombstone last month. *Don't go trying to doctorate yesself,* neither. It's that Monday melancholia you've got, but don't let it make you morbitious. Always look on the bright side. What does it matter if ye've had fifteen operations already? Ye can still *breethe* can't ye? Still open yer eyes, eh? Well, wot are you *worryin'* about? If Dr. Gargle can't cure your depresshun, ye might as well shoot yesself. Take my hadvice, Mrs. Pinkle. Halter your outlook. Life's like a pin—there's always a point to it if you look hard enough. Ha, ha! Oh, ye've heard that one? *(Pip . . . Pip . . . Pip . . .)* That's my three minits oop. Remember Cooee! Aye, the French one, that's right. 'Bye, now."

* * *

I was pleased to learn in these columns some time ago that phenobarbitone has supplanted the policeman as bogyman of the nursery, for policemen are such kindly men. There was that one who brought an old lady into the mental observation ward because she had been having a noisy conversation with an alarm clock in a busy shopping street. He brought her clock along too. "What's that," I inquired, "evidence?" "No," he replied sheepishly, "I thought it might be company for her."

* * *

News from School.—"The other day I was electrocuted with 70,000 volts and all my hair stood on end, sparks came out of my nose and feet, and I lit a bunsen off my finger. It was terribly queer. On the Merit Half on Tues. two other boys and I nickel-plated some halfpennies and I copper-plated my scissors. The same afternoon we took some stereoscopic photos and in one we had to sit absolutely still for 15 seconds. Then we went and had tea with Mr. S. and made a lot of toast on the fire."

Letters to the Editor

THE TREATMENT OF PEPTIC ULCER

SIR,—You have several times let me say my piece, and I had not intended to intervene again. Comments on the paper by Dr. Doll and Dr. Pygott have, however sapped my resolution. The shrewdest observer, lacking a training in mathematical logic, lets himself be outwitted by the prestige of the M.R.C. statistical unit and a nimble use of χ^2 and p. Dr. Doll has sold the three main dummies of statistics—those hoary fallacies which Prof. R. A. Fisher has repeatedly castigated.

The first dummy was bought by Dr. Todd (Feb. 16) There is a distinction between a therapeutic trial where a counter-measure against a single invader is tested, and a trial in which we treat the patient and attempt to increase his resistance. In the first case it may be justifiable to use a simple design because we assume the homogeneity of the invader. In the second case no statistical design has any practical value unless it tests the possibility that different individuals react differently. Neglect of this principle can lead to absurd conclusions. A recent American paper purported to show to several places of decimals that bran had neither a good nor a bad effect on the human colon. Fortunately the experiment was well designed, and by using more appropriate mathematical methods it was easy to show that bran had a highly significant effect; some of the subjects were *markedly better during the "bran periods,"* some markedly worse; it was only the average which remained unchanged.

Phenobarbitone on the *average* has no *measurable* effect in Dr. Doll's series. Does this mean anything at all? Some gastric ulcer patients are depressed and need stimulating. A few are over-energetic or full of pathological anxieties. In the one group phenobarbitone seems harmful or dangerous; in the other it seems to help. If it is used as a routine in a small series the good and bad effects cancel out, and the new type of logic which the medical press now favours tells us that there is no significant effect.

The second dummy has sold better to clinicians than to radiologists. It is an axiom of science that before making a measurement one measures the yardstick. Dr. Doll, in the teeth of evidence to the contrary, assumes that the area of the X-ray niche can be used to measure the size of the crater. The wisdom of our fathers gets buried in the basement; *their folly lives on* in the humour of the iconoclast. In the first decade of this century most bright young men in European university medical clinics took an interest in radiology. Films were taken before gastrectomy and compared with the specimen. The radiologist's diagnosis of a large penetrating gastric ulcer was found repeatedly to be wrong. The modern explanation of the discrepancy was first put forward by Haudek in 1912. At the 16th German Radiology Congress in 1925 Forssell, Berg, and other leading radiologists supported his views. Gutzeit [1] added further evidence. The late A. E. Barclay [2] claimed to have come to the same conclusions quite independently. Numerous modern French contributions accept the Haudek phenomenon as a matter of course. Many X-ray niches are not ulcers but pseudo-diverticula formed by a ring contracture of the muscularis mucosæ. In others the apparent depth is due to surrounding œdema. In Barclay's words: "An ulcer can be diagnosed radiographically but it is not yet possible to be certain whether it is penetrating or a mere erosion."

The final fallacy is the most serious of all. What right have we to generalise from Dr. Doll's results? This was not a Gallup poll sample. What actually happened?

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1. Gutzeit, K. Die Gastroskopie im Rahmen der klinischen Magendiagnostik. Berlin, 1929.
2. Barclay, A. E. The Digestive Tract. London, 1936.

During an unstated period of time certain general practitioners sent an unstated number of patients to the Central Middlesex Hospital. There they were seen by an unstated number of unnamed clinicians who for unstated reasons referred an unstated number for a barium meal. The barium meal was done after an unstated interval in which some ulcers possibly healed. An unstated proportion of the patients with gastric ulcers was then brought into the ward after an unstated interval and the trial commenced. No-one can say how difficult the cases were, but 27 out of the 64 ulcers were 20 sq. mm. in area or less—i.e., allowing for X-ray magnification, almost healed. Dr. Doll was then very unlucky in his randomisation. Only 8 out of 27 small ulcers fell into the inpatient group, and only 3 out of 12 big ones fell into the outpatient group. A conventional régime with mild variants was applied, and, as happened when I used to use this régime many years ago, results were poor. 4 of the 8 small ulcers treated in the ward, and 8 of the 19 treated at home, got larger. Only 5 of the ulcers over 20 sq. mm. in area got larger, and of these 2 had been treated in the ward and 3 at home. Of the 15 medium-sized ulcers treated in the ward 6 were apparently healed after three months, whereas of the 10 home-treated ones only 1 was healed.

Am I supposed to read these figures and change my ideas? Should I return to a discarded mode of treatment and again recommend milk, slops, and rest, when for several years I believe that I have got better results by trying to keep patients at work and on a normal diet? Dr. Doll's experimental design does not touch my problem. I repeat to him, and he knows that my records are open to inspection, that there is a reason for most gastric ulcers, and if you can get rid of the cause the ulcer will heal and remain healed for long periods. If you do not get rid of the cause there is probably a 75% relapse-rate. The way to find the cause is to treat the patient at work on his ordinary diet, and in his ordinary environment. Our job is to help the patient to get his confidence back, to find out how to live fully, to be happy, and to have a good appetite and a normal bowel motion without aperients. If we can do that, there is no ulcer problem.

In one matter Dr. Avery Jones (Feb. 9) and I agree. The right solution for this kind of controversy would be for patients to be allotted at random between Dr. Doll and myself, and for an independent committee to assess results. A single clinician cannot carry out a randomised trial by himself. He cannot be expected to forgo the right to give his best to each individual patient.

Peptic Ulcer Clinic,
Medical Unit,
London Hospital, E.1. DENYS JENNINGS.

SIR,—Dr. Avery Jones (Feb. 23) is a little unlucky in his choice of an example. Starvation can hardly be described as the "old and traditional way" of treating hæmatemesis. Rather, it was the outcome of theory triumphing over experience; and this, I imagine, is what Dr. Todd is really criticising. Early writers emphasised the importance of feeding and of administering morphine, and when starvation was introduced Lenhartz protested against it. A decade later he received quite a lot of support. Between 1905 and 1910 Langdon Brown of St. Bartholomew's, F. J. Smith of the London, and Edmund Spriggs of St. George's were all advocating early feeding, or the "Lenhartz method" as they called it. Similarly, they all recognised the importance of age in prognosis.

Spriggs[1] gave a full bibliography of this interesting chapter in medicine, and more recently Alvarez[2] has tried, in his own words, to "put the record straight." Like Carroll's Red Queen, we have to run very fast to stay in the same place.

Surgical Unit, London Hospital, E.1. J. E. RICHARDSON.

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1. Spriggs, E. *Quart. J. Med.* 1911, 4, 399.
2. Alvarez, W. C. Editorial, *Gastroenterology*, 1946, 6, 324.

SIR,—I read with interest Dr. Todd's article of Jan. 19.

Even if we agree that duodenal ulcer is a stress disease, experience shows that only a small proportion of patients are likely to benefit from psychotherapy. Promising, above all, are those who after a few interviews recognise that deep down in their minds they have been desirous of altering the habitual pattern of their aiming. But adequate treatment requires a special technique which is neither simple encouragement nor orthodox psychoanalysis.

Rest in psychosomatic ailments helps through reducing the factor of effort. A large number of patients, however, are of the type that follow to excess the human practice of forestalling in fantasy possible failures, and planning imaginary compensations for frustrations. The medical advice to rest justifies inactivity and should implicitly also encourage relaxation in mental efforts, conscious and unconscious. If the mind will not accept the dispensation, the patient cannot benefit by, and may even be the worse for, rest in bed. Most sufferers from hypertension unconsciously interpret the advice to rest as a discouragement and threat, and remain tense if confined to the sickroom. Duodenal patients in general are of a different kind. Many, however, cannot forgive themselves for indulging in idleness, while others are too competitive to accept a reduced level of striving and enjoying; others again will not acknowledge their nervous and affective limitations. In some cases the vegetative overactivity is not, in fact, closely associated with the prevailing stresses of life, being rather a strictly physiological disorder. With experience one might be able to distinguish this type of patient and spare him the unpromising psychological procedure.

Psychotherapy in duodenal ulcer can, therefore, be only an adjuvant measure, though in some cases admittedly a very important one; diet, rest, and pharmacological treatment will remain the general methods of cure in this condition.

London, N.W.4. S. LOWY.

HYSTEROSALPINGOGRAPHY IN FEMALE INFERTILITY

SIR,—Though 'Viskiosol Six' has been used quite extensively in my department I have no doubt that the 35% diodone solution chosen by Dr. Preiskel and Dr. Pollock is just as satisfactory as a contrast medium, and I appreciate that as this is a more dilute solution it may well have advantages in being less irritant.

Their technique differs most from the one I adopt in that they are content to see what they have done and I prefer to see what I am doing. I agree that they expose their patients to a few röntgens less, but I cannot agree that a technique involving a short screen examination need expose the ovaries to a dose of 30 r. Such a dose involves about half a skin-tolerance dose if delivered at normal screening kilovoltages.

As for under-couch versus over-couch radiography, I would point out that the inverse-square law operates to reduce the length of exposure necessary to produce an adequate image on the film at the nearer distance, just as it also operates to increase the intensity of the radiation received. The net effect is not greatly in favour of either side. I should add, too, that for other reasons under-couch tubes are now being set back further from the couch top to distances almost equal to those used in normal over-couch work. Those in my department are set back 30 in. from the screen contact with the patient.

With this plea of mitigation, I feel that I can face the geneticists with a modicum of confidence.

Central Middlesex Hospital,
London, N.W.10.

F. PYGOTT
Radiologist.

A.C.T.H. BY SUBCUTANEOUS "DRIP"

SIR,—So far we have seen no reference to the administration of A.C.T.H. by subcutaneous or intramuscular "drip," though no doubt it has been given by this route. Recently we have given 8-hour drips daily for twenty consecutive days with relatively little discomfort to the patient (0·25 ml. of 'Hyalase' was added to each 300 ml. infused). There is no need to point out that this route is greatly to be preferred for many patients.

Sheffield Centre for the
Investigation and Treatment of
Rheumatic Diseases.

H. F. WEST
G. R. NEWNS.

EXPEDITION TO GREENLAND

SIR,—The British North Greenland Expedition will leave England in July, 1952, and will probably remain in the field for two years with a relief expedition in the summer of 1953. The expedition will consist of some 24 members, approximately half being Naval officers and half civilians, including geologists, meteorologists, and glaciologists; it is hoped that 50% of the party will be able to remain for the second year. The committee organising the expedition has agreed that, in addition to a medical man, a physiologist should be appointed. Hitherto in the history of Arctic and Antarctic exploration no professional physiologist has accompanied an expedition, and although many useful observations have been made on the effects of long-continued life in the cold on man, no systematic information has yet been obtained.

There is no doubt that the decision to include a physiologist represents a most valuable opportunity for those interested in problems of human physiology. Would anyone interested in becoming a member of the expedition get in touch with me?

Department of Physiology,
University College,
Gower Street, London, W.C.1.

G. L. BROWN.

HICCUP DURING ANÆSTHESIA

SIR,—Hiccup during anæsthesia was very rare before muscle relaxants were introduced, but now it is commonly observed by anæsthetists who use relaxants for upper abdominal and thoracic surgery. Here its production is often associated, as Dr. Tobin (Feb. 16) points out, with traction on the œsophagus, with manipulation, and with rough handling. It is less common with thiopentone alone; but it is more likely to occur if there be co-existing peritonitis, especially peritonitis associated with perforation of peptic ulcer.

Muscle relaxants block the reflex arc at the myoneural junctions in the skeletal muscle of the diaphragm, so that afferent impulses from the respiratory centre can no longer produce rhythmic contractions; yet hiccup can still occur. Hiccup is seen with "assisted" respiration (not "controlled" respiration, as Dr. Hunter Smith describes it in his letter of Feb. 16). Since the muscle relaxants do not produce respiratory arrest but merely prevent skeletal muscle from responding to an afferent stimulus via its motor nerve, the reflex pathway must be blocked elsewhere; and the anæsthetist has no choice but to deepen the narcosis.

Because of the need for very rapid depression only two agents can be of any value; (1) thiopentone, which can be dismissed because, though rapidly acting, in small dosage it may itself produce hiccup while in larger dosage it would prolong narcosis unjustifiably; and (2) cyclopropane, which acts rapidly and is eliminated equally rapidly. The exhibition of a mixture containing oxygen and a very high percentage (90%) of cyclopropane, while continuing to assist respiration and to invoke the aid of the Hering-Breuer reflex, will terminate hiccup in every instance within 2–3 minutes, when the use of cyclopropane can be abandoned. I have used this method since early in 1947. The use of cyclopropane in such a fashion is, however, not free from danger; there is the risk of myocardial failure from ventricular fibrillation, and there is the risk of explosion. The former danger can be averted by administering 20 ml. of 1% procaine hydrochloride intravenously—a procedure which occupies only 10 seconds if a Gordh needle or an intravenous transfusion is in use.

Hiccup can be prevented, too, by a similar method, though this is not so consistently successful. Briefly, instead of depending for anæsthesia on the thiopentone/muscle relaxant/nitrous oxide and oxygen sequence alone, about 2% of ether is included with the inspired mixture, and respiration is assisted. This will usually depress the central nervous system far enough to prevent hiccup.

I make no claim to originality in these methods, which are derived from listening to and working with skilled anæsthetists.

Institute of Dental Surgery,
Eastman Dental Hospital,
London, W.C.1.

JOHN HENDRIE.

SIR,—Dr. Fayerde (Feb. 2) and Dr. Tobin (Feb. 16) have both expressed the view that the onset of hiccup was unrelated to the level or depth of anæsthesia during the operation of gastrectomy. Surely we cannot take this literally. Dr. Tobin himself says that only those cases in which great traction was exerted on the stomach developed hiccup, and it would appear that in these cases anæsthesia was not deep enough.

In a series of gastrectomies with anæsthesia by thiopentone, d-tubocurarine chloride, cyclopropane, and oxygen, hiccup was very rare. On the other hand, this was not so in a series anæsthetised by thiopentone, tubocurarine, nitrous oxide and oxygen (2 : 1), and controlled respiration; here hiccup occurred when the stomach was pulled on in order to tie the left gastric artery. The hiccup disappeared, as in Dr. Lee's experience (Feb. 16), by introducing amyl nitrite into the circuit. Hiccup has been forestalled by adding cyclopropane to the gas-oxygen mixture, or by giving 2–4 ml. of 5% thiopentone and/or 3–5 mg. of tubocurarine about five minutes before the left gastric artery was tied.

It would seem, therefore, that hiccup occurs under anæsthesia which is inadequate for the strong stimulus of pulling on the stomach.

Edinburgh.

LEON KAUFMAN.

INDUSTRIAL DERMATITIS

SIR,—Of the 935,007 people who up to a short time ago had been registered under the Disabled Persons (Employment) Act, 1944, only 9512 (1%) were disabled by skin disease; and thus the 3 cases of skin disease that Dr. Bourne reports (Feb. 16) as having been seen by the Tottenham Medical Interviewing Committee in a series of 192 registered disabled persons accord with the national incidence. An investigation into the dermatological aspects of unemployment and resettlement[1] reveal that persons on the disablement register on account skin disease were fairly evenly distributed througho England and Wales.

It seems paradoxical that so few sufferers from sk disabilities are registered as disabled persons, eve though certified industrial dermatitis is one of the mo important causes of industrial injury. Industrial derma titis has many facets and attracts the attention of a wi variety of professional bodies. Hopes were raised th the Industrial Injury Act, 1948, with its extensiv provisions, might be applied to coördinating thes bodies, clarifying the extent and distribution of th disorder, and contributing to its prevention and ultimat elimination. Unfortunately the opportunity for resolute action afforded by the Act appears to have been missed. The malady and the confusion surrounding it remain almost unchanged.

Department of Dermatology,
United Bristol Hospitals.

MARK HEWITT.

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[1] Hewitt, M. *Lancet*, 1950, ii, 921.

PSYCHOSOMATIC SYMPTOM FORMATION

SIR,—It is interesting to note that Dr. Macalpine (Feb. 9) considers that it is unjustifiable to transcribe physiological happenings into the jargon of psychology. On the other hand, however, might not one employ physiological concepts to explain some of the manifestations of psychosomatic pathology—or should one say "psymptoms"?

Some fifty years ago Sherrington described the process of integration in the central nervous system. The cortical representation of an integration centre is independent of the origin of stimuli reaching that centre—hence referred pain. Might not integration centres exist which receive afferent impulses from both somatic and cortical sources? Psychological treatment, by reducing the cortical stimuli, could relieve the manifestations; but these might well return with an increase in somatic stimuli due to an organic lesion.

Dr. Macalpine quotes the case of a patient who said that her condition was worse when she was hot. Was it really necessary for her to be both hot and bothered? The habitué of a Turkish bath is well aware that autonomic responses follow the application of heat, unless, of course, he cannot be bothered to go into the hot room.

Department of Surgery,
Royal Infirmary,
Manchester.

A. HALL RATCLIFFE.

BARBITURATES ON THE BRAIN

SIR,—I am glad of your timely annotation last week on the barbiturate menace. I think, however, that there are probably more addicts among practitioners in prescribing them than there are among their victims in taking them. I am constantly meeting patients who have been having "phenobarb." daily for years—the record, I think, being seven—without any real justification. One realises that this drug, useful as it perhaps is for a few weeks at a time, has become the panacea among doctors the moment they are faced with a person having functional troubles. If he is excited, they give him "phenobarb." If he is depressed, they give him "phenobarb.," and then perhaps have to add amphetamine to neutralise this, so that the patient has a double dose of poisons.

Surely the maxim *tolle causam* applies here as much as anywhere else. The cure for psychoneuroses is to tackle them where they originate, in the mind. To depress the nervous system is no way to deal with "nerves," any more than soft-pedalling the pain with morphine is the way to deal with acute appendicitis.

Perhaps I feel particularly strongly about this. But so much harm is done in cases where a few weeks or months of adequate psychotherapy would result in permanent cure, that I may perhaps be justified.

London, S.W.3.

L. J. BENDIT.

INCUBATION PERIOD OF INFECTIVE HEPATITIS

SIR,—Questions of priority are not as a rule of great moment when applied to medical discoveries, but it may be worth noting that the correct incubation period of infective hepatitis was first demonstrated by W. G. Booth and C. C. Okell in 1927–28.[1] Their results were confirmed by Pickles[2] in Yorkshire, and by Findlay, Dunlop, and Brown[3] in Surrey. The latter observers deduced the incubation period of infective hepatitis not only from observations in the field but *in corpore vile*, for Major H. C. Brown became infected in the laboratory while handling sera sent for examination from Yorkshire by Dr. Pickles. This was the first evidence that a hepatitis virus was present in the serum, and also the first example of a series of laboratory infections now recorded among those who have had to handle blood and its products. Early observers also demonstrated what has again been shown by Dr. H. S. Brodribb—in your issue of Feb. 16—that cases in a family or institution tend to occur in small batches at monthly intervals, suggesting that as a general rule the period of infectivity of a patient is comparatively short.

It is not without interest that in an attempt to determine the early incidence of jaundice among British officers and other ranks serving in West Africa during the war it was found that officers had had a significantly higher morbidity-rate in childhood and adolescence than other ranks.[4] The higher incidence in officers could be correlated with their more common residence in boarding-schools, where in most cases the disease had been contracted.

Radlett, Herts.

G. M. FINDLAY.

AN UNUSUAL EPIDEMIC

SIR,—I am most interested in your annotation (Feb. 9) on the cases of "acute labyrinthitis" and in Dr. Worster-Drought's excellent description (Feb. 16). In the last eighteen months I have seen 9 such cases, which exactly fit this pattern. I would, however, be very hesitant about ascribing them to infection. My cases have been widely scattered over Devon and Cornwall (Truro 2, St. Mawes 1, Plymouth 1, Torquay 2, Kingsbridge 1, Ilsington 1, Sidmouth 1), with no connection between each other. None of the patients has been pyrexial and the cerebrospinal fluid in the 2 cases where it was examined was normal.

One patient was of interest in this connection as she had been confined to bed for the previous three weeks with sciatica; this did not suggest an infective agent. The patient, a woman aged 59, also had a history of a previous episode eight years earlier—the only case where there had been any similar attack before.

I have tentatively regarded these cases as of vascular or vasomotor origin. The striking thing about them is the absence of any cochlear dysfunction—a point which makes most of my otologist colleagues reluctant to consider them labyrinthine in origin. I feel, however, that their sensitivity to sudden changes of posture, as mentioned by Dr. Worster-Drought, is very convincing evidence that this is in fact the site of the disturbance.

Exeter.

N. S. ALCOCK.

SIR,—Your annotation of Feb. 9 on acute or epidemic labyrinthitis has brought to notice a condition which has previously received little recognition. I have met four such cases during the past six months.

The patients' ages were 22, 29, 30, and 41. In each instance there was a history of acute attacks of vertigo, made worse by any movement of the head and accompanied by staggering to one side or falling. Two patients vomited, and one preferred to lie on the unaffected side. Though not observed in an attack, one showed a vestibular tilt of the head and another nystagmus when seen later. One had noticed hypersensitivity to some sounds; but none had had tinnitus, and none had deafness or other aural symptoms. There had been no clouding of consciousness and no nasal catarrh. The tympanic membranes were intact, and normal inflation was noted shortly after an attack in one case. The vertiginous attacks were always sudden in onset and brief in duration (lasting for a minute or less). Attacks recurred for either a few days or a few weeks, and the patients tended to lose confidence when out of doors and feared falling. Two complained of dull headache. Examination of the cerebrospinal fluid in one of these showed only 2 lymphocytes per c.mm. and 60 mg. protein per 100 ml. The patients were in different families.

The condition seems to be infective rather than infectious, and produces a temporary irritative effect upon the labyrinth or vestibular nerve. The good prognosis, the absence of cochlear involvement, and the comparative youth of the patients especially distinguish the condition from Ménière's disease.

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[1] Booth, W. G., Okell, C. C. *Publ. Hlth*, 1927–28, 41, 237.
[2] Pickles, W. N. *Brit. med. J.* 1930, i, 944.
[3] Findlay, G. M., Dunlop, J. L., Brown, H. C. *Trans. R. Soc. trop. Med. Hyg.* 1931, 25, 7.
[4] Findlay, G. M., Martin, N. H., Mitchell, J. B. *Lancet*, 1944, ii, 301.

London, W.1. ERIC C. O. JEWESBURY.

SIR,—Between Dec. 26 last year and the end of January I saw four cases of acute labyrinthitis. I myself was the first case. The onset was quite sudden, without deafness or tinnitus and with very mild nausea. True vertigo was induced only by sudden change of posture—and this only after some time in one position. I was able to continue working, and was free of symptoms in ten days.

One case was in a man of 72, who had vomiting and nystagmus for forty-eight hours and recovered completely in ten days. In the other two cases the attacks were even milder than my own. My three partners have seen two cases in this epidemic.

Cheshunt, Herts. JOHN A. CURRIE.

SIR,—During a period of six weeks in December, 1951, and January, 1952, 4 cases of acute labyrinthitis occurred in my general practice. There was no apparent social or family connection between any of these patients, and they all lived some distance from one another.

The 1st case was seen on Dec. 4, the 2nd on Dec. 10, the 3rd on Dec. 24, and the 4th on Jan. 15. The patients were 2 men, aged 55 and 42, and 2 women, also aged 55 and 42. They were all fit. In 2 there was a history of old middle-ear disease, but this appeared to have been quiescent for some years. There was no history of any associated coughs or colds in any of the patients, nor in other members of their households.

The onset was dramatically sudden; in all 4 the symptoms were first noted in the morning after a normal night's sleep. The vertigo did not commence on waking but only when the head was raised off the pillow; if the head remained still there was little discomfort. In the 2 severe cases the patients had to remain in bed, but the other 2 were able to walk around the house.

These patients had true vertigo, aggravated by movements of the head and changes in posture. Vomiting occurred in the 2 severe cases. Tinnitus and deafness was not noted by any patient. The only abnormal physical sign was nystagmus of labyrinthine type, which was present in all 4 cases. In the 2 older patients there was moderate hypertension (185/100 mm. Hg). There was no fever or tachycardia.

The condition resolved spontaneously in 6–21 days. In all 4 the symptoms abated within 4–5 days.

Beckenham, Kent. JOHN FRY.

PSYCHOLOGY AND THE MATERNITY UNIT

SIR,—Dr. Dick Read (Feb. 16) shows impatience in saying that we are "withholding" fearless labour. To provide it not only takes time and trouble but also an understanding of the technique. Those who imagine that "natural childbirth" is the "natural" residue left after fears have been abstracted will not get Dr. Read's results; they will merely observe that the patient is well-behaved.

In so-called "natural childbirth" a certain pattern of labour does emerge, but it is not precisely "natural" any more than is the skill and concentration of a craftsman. Natural childbirth is labour governed by an induced cerebral complex, formed and confirmed by what is more usually described as treatment by suggestion. It is the thought-confining and heart-warming effects of suggestion that secure excellent results.

The characteristic procedures in suggestive treatment are as follows:

1. Reduce the field of attention; remove fears and aversions; simplify concepts of process and duty in labour. Dr. Dick Read's mottoes serve well to "bind the mind" to simple ideas of action.

2. Reduce distractions in the field of observation—i.e., control the circumstances. Use care not to arouse the combative attitude, anger, or uneasy self-consciousness in the patient. The mind must be "free to attend" to duty.

3. Energise idea-process emotionally in the formed field of attention and observation. Hospital or consultant prestige, high fees, or trouble taken for no personal profit, public repute and previous successes, insight, sympathy, emotive *words, and careful phrasing, &c., all* tend to induce emotional intensity in belief in the instruction given, and in liking for and belief in the doctor qua medical attendant. The patient naturally has the wish to believe good news.

4. Reinforce the whole complex by inducing relaxation. Relaxation should be hetero-induced to be sensed as full or self-perpetuating. Self-induced relaxation is seldom full relaxation, and incomplete relaxation with dispersed attention does very little to reduce pain. Summary suggestions should be given to the patient when in the fully relaxed state. In this bodily state the mind is receptive or non-combative, impressionable, attentive without effort, and sufficiently retentive.

On these principles, if one takes the trouble, one can rival the results of Dr. Dick Read. Direct or "hypnotic" suggestion in an uncertain number of cases is more effective in quite abolishing pain, but indirect or "waking" suggestion is more educative in fortitude, self-respect, and maternal love and pride.

London, E.13. W. THOMSON BROWN.

REQUEST FOR SPECIMENS OF JAWS

SIR,—The Medical Research Council's Dental Research Unit is in urgent need of certain post-mortem material for its investigations into dental and associated disease. In particular, the jaws, or parts of jaws, with teeth in situ, are required from healthy mouths; from cases with gingivitis but no other specific lesions; from cases of ulcerative stomatitis; and from epileptics formerly under 'Epanutin' (sodium diphenyl hydantoinate) control.

When any of the above material is or is likely to become available, it is requested that this unit be notified (tel., Brixton 4744). Arrangements will then be made to collect the specimens which, if possible, should be removed and fixed in 10% formalin soon after death.

Medical Research Council,
Dental Research Unit,
King's College Hospital Medical School,
Denmark Hill, London, S.E.5. J. J. D. KING.

SLOW-RELEASE MEDIUM FOR A.C.T.H.

SIR,—The report by Mr. Bruce and Dr. Parkes (Jan. 12) prompts us to describe work on a new long-acting A.C.T.H. preparation which has been going on for some time in Norway. A preliminary report on the clinical effect of this new preparation ('Cortico-Depot Nyco') was given by Forbech[1] at the Second European Congress of Rheumatology in Barcelona last year; and further reports are to appear in the near future.[2] [3] We shall therefore comment very briefly on our experiences.

The long-acting A.C.T.H. preparations have been hitherto evolved[4] on one of two principles: (*a*) suspension of A.C.T.H. adsorbed to aluminium phosphate, or (*b*) suspension of A.C.T.H. in hydrophobe media (oils).

Our preparation is based on a different principle. Cortico-depot is a suspension of an A.C.T.H.-zinc-protamine complex in an aqueous phosphate buffer (pH 6·5–7·0). The sterile suspension is characterised by high suspensibility and low solubility; about 98% of the activity is present in the suspended particles, and only 2–3% in the aqueous medium. No decrease in activity has followed storage at room-temperature for 8 months. The A.C.T.H. used in cortico-depot was prepared from the anterior lobe of whale's pituitary.

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1. Forbech, V. *Farmakoterapi*, 1951, 7, 98.
2. Forbech, V., Holtermann, H. *Nord. Med.* (in the press).
3. Solem, J. H. *Ibid* (in the press).
4. Wolfson, W. Q., Thompson, R. E., Robinson, W. D., Duff, I. F., Cohen, C., Lewis, L., Haut, D. Proceedings of the Second Clinical A.C.T.H. Conference. New York, 1951; p. 1.

We have administered this preparation to 7 patients –4 with chronic rheumatoid arthritis, 1 with severe hronic asthma, 1 with pemphigus vulgaris, and 1 with cleroderma.

We have been primarily interested in recording the clinical fficacy of the drug. Patients were therefore selected who ad nearly constant symptoms and signs and who gave a redictable response to A.C.T.H. of known potency (corticoropin 'Nyco'). The patients were all well known in the ward. Initially they were treated with corticotropin by slow intravenous drip in 5% glucose solution, daily for 6–8 days until a satisfactory clinical response was obtained. Suppression of the various symptoms continued when the ntravenous infusion of corticotropin was replaced by intramuscular administration of cortico-depot.

In all patients the eosinophil-count after 20 I.U. of cortico-depot intramuscularly did not return to pre-treatment level until about 36 hours after administration. The symptoms were, however, satisfactorily controlled for 3 days after each injection. Treatment is now continued with 20 I.U. of cortico-depot at 72-hour intervals, and these 7 patients are all doing well.

In 3 cases intervals were successfully increased to 4–5 days during their stay in the ward; but on their return to increased activities at home a maintenance dose every 3rd day was required.

It is encouraging that the urinary excretion of 17-ketosteroids did not exceed normal upper limits on administration of the maintenance dose mentioned above, suggesting that only moderate side-effects may follow long-continued administration of cortico-depot. During treatment with this substance no special precautions have been taken to prevent fluid retention, of which there has been no clinical evidence in our group. From a practical point of view it is important that even doses of as much as 10 ml. (200 I.U.) intramuscularly have given rise to no local irritation. The preparation is easy to handle and inject.

Medical Department,
Drammen Hospital, Norway. J. H. SOLEM.

Biochemical Department,
Oslo Nyegaard & Co. A/S, Oslo. HUGO HOLTERMANN.

DEAFNESS IN CHILDHOOD

SIR,—The leader in your last issue states many facts not always appreciated by persons—medical, educational, and lay—who have not studied the problem of training deaf children. I should also like to support Miss Edith Whetnall's plea for the provision of training facilities for very young children: among their needs are a small "monopack" type of hearing-aid to replace the cumbersome 'Medresco' aid, if a commercial one cannot be afforded.

I should like to point out, however, that Miss Whetnall's important letter may be misconstrued unintentionally, in that the number of young deaf children she mentions seems very small—only 89 in London nursery schools for the deaf, and 75 from Southern England receiving auditory training. These figures may give the impression that the problem involves only a minute proportion of the child population, and is therefore not worthy of as much attention as other forms of disability. I should like to emphasise that in Britain there are known to be at least two deaf children in every thousand; and besides these there are certainly others not diagnosed—as will be discovered when vigilance on "backward" children is improved outside a few centres.

The setting-up of many more training centres would enable young children, at the age when language is acquired, to go to day-nursery and ordinary schools, and then return home for contact with parents and the hearing public. This would obviate the increasing tendency only to open more residential schools, where "contact" in out-of-school hours is negligible: only six hours a day can be spent with teachers. There is no doubt that some residential schools are necessary, but in them there should be a great many "off duty" persons to help impart knowledge.

The difficulties which many authorities, doctors, and parents in the provinces have in finding facilities for dealing with a suspected or definitely deaf child are still depressingly large and multiple. Considerable help may be given by the Deaf Childrens' Society, which, as mentioned by Mr. Owen a few weeks ago, has formed an efficient information bureau.

London, W.1. IAN G. ROBIN.

NEEDS AND MEANS

SIR,—I was interested to read Dr. Barrow's remarks (Feb. 16) concerning the new health service charges. It is indeed consoling to see such altruism still left amongst members of our profession. But I am amused to see the anxiety which assails our colleagues concerning these new charges. Why not coal, food, and houses free?—things far more important than a medical service.

As I see it, hope only lies in one direction. This service must be placed, like the Crown, above politics. Furthermore, a percentage charge should be made for all services given, even though, as a result, the football pools, the cinemas, and the manufacturers of television sets might suffer a little. It is about time we realised that we are bankrupt and behaved accordingly.

Rugby. P. J. O'REILLY.

SIR,—In my opinion the shilling prescription may be the cause of an increase in suicides in the months to come.

From March onwards patients are practically certain to ask for double or treble supplies of their favourite sedative. It will save their shillings and the doctor's time if he grants their requests. But there may be some to whom a full bottle of an attractive barbiturate proves too great a temptation. In my experience it is the patient who has somehow managed to obtain fifty or a hundred of his night tablets who takes an overdose, practically never the one who gets a dozen or so at a time. Psychiatrists probably know the real reason. Time and again it happens, and somehow it must be prevented.

Exmouth. ARMOREL NETTELL.

INDUSTRIAL HEALTH SERVICES

SIR,—I am very grateful for Dr. Herford's comments last week on my letter of Feb. 9. Those of us who have enjoyed the hospitality of the Slough Industrial Health Service will agree that it is a model of its kind.

The service I envisage would be a combination of an inspection and advisory service for the factory, together with a clinical and rehabilitation service for the workman. In a closed area such as the Slough Estate this has been largely achieved, save where outside authorities exercise statutory powers. It would appear possible for a local authority to organise a comprehensive industrial health service under section 28 of the National Health Service Act, and I am extremely sorry that advantage was not taken of this when we set up twelve model factories on a new municipal trading estate a couple of years ago. The medical staff would have consisted of a whole-time industrial medical officer and the appropriate auxiliaries, housed in a specially designed clinic on the lines of Dr. Herford's establishment. A close liaison would have been established with the local hospitals and practitioners. The mixed group of factories would have acted as a small industrial-medicine laboratory.

Such an organisation, operated under the control of the medical officer of health and linked intimately with the other local health authority services, including an adequate interpretation of "prevention, care, and aftercare," would leave only the special commitments of the medical inspection of factories outside the local-authority service. The next step would be to turn over the responsibility for inspection to an adequately qualified whole-time local-authority industrial medical officer and treat the medical inspector of factories as a regional consultant.

My information is that the total establishment of medical inspectors of factories is only sixteen for the whole country, and that this establishment is not full. They have to cover all London, 61 counties, 83 county boroughs, 309 non-county boroughs, and 1047 district council areas, each of which has a medical officer of health and a sanitary inspector and the appropriate extra staff for the bigger units. I really cannot see how the present number of medical inspectors can do the work adequately. I would repeat that industrial health does not stop at the factory gate, and I would quote the work of the county medical officer of Northamptonshire on the problem of tuberculosis in the boot and shoe industry as a model example of how the unique facilities of the medical officer of health can be used in industry.

Brighton. W. S. PARKER
Medical Officer of Health.

CAT-SCRATCH FEVER

SIR,—I read with interest Dr. Cox's letter (Feb. 16) concerning a case of cat-scratch disease seen at the Hospital for Sick Children, Great Ormond Street, in which a skin test performed with an antigen supplied by Prof. P. Mollaret was positive.

This antigen is not, as Dr. Cox suggests, *specific* to cat-scratch disease; apart from the question of false positive results, it will give cross-positives with members of the psittacosis/lymphogranuloma-venereum/trachoma group.

An opportunity has been taken of testing this antigen, also supplied by Professor Mollaret, on a few cases of non-specific urethritis, which disorder is believed to belong to this group of virus diseases. Six patients with untreated or recently treated non-specific urethritis, and one untreated female consort, were tested. There were three positive results, with papules 6 mm. or more in diameter. Three controls gave negative results.

One certainly cannot say, therefore, that the skin test is "specific" to cat-scratch disease, and that a positive result necessarily indicates that the patient is suffering from it.

St. Mary's Hospital, London, W.2. R. R. WILLCOX.

BASIC RESEARCH INTO CONTRACEPTION

SIR,—Prof. Hugh Nicol (Feb. 9) has used my letter to you (Jan. 5) as a peg on which to hang an interesting but not strictly relevant discourse on fertiliser policy. He appears to be criticising me for optimism and complacency; to some extent he is right. But, although in fact I agree with much of what he says, I do not think the case is unequivocally established. My own argument was about the need for more research on contraception; I preferred to err on the conservative side and state the case in such a way that no-one could criticise it as alarmist. If Professor Nicol is right it is even more necessary to limit the population, and I am sorry that he makes no suggestions about how this should be done.

Much the same comment applies to the casuistry in Mr. Preece's letter (Jan. 26). People, and before them animals, have been outbreeding the food-supply for a considerable time. But those who, whether from reading Malthus or for other reasons, have been aware of this have hitherto lived in the favoured communities that were able to breed relatively freely and still find extra food for the extra mouths. Some time—Professor Nicol says some time soon—we are going to lose this enviable distinction. All the peoples of the world will then be in the same predicament. Most of them do not have the research organisation needed to find even a partial solution to the problem. It is this fact, rather than pure self-interest, that should lead us to recognise the need for more basic research on the gametes.

Rothamsted Experimental Station,
Harpenden, Herts. N. W. PIRIE.

MEDICINE WITHIN THE ATLANTIC COMMUNIT

SIR,—In his interesting survey (Feb. 16) Dr. Meiklejoh refers to the exchanges which are annually arrange between senior members of the staffs of Johns Hopki and Guy's Hospitals. It may not be so widely know that in addition there is an exchange of registrars betwee Guy's and Columbia. Further, "cultural contacts have been established at the undergraduate level b the admission of medical students from Duke Universit North Carolina, to pædiatric courses at both Guy and St. Bartholomew's.

It has been possible to find places at Guy's for thes students only during the summer quarter, which is pity, for the number of applicants from Duke has treble this year. It would seem particularly desirable that better understanding should be fostered between th junior members of the Atlantic Community. Unfortunately for British students financial stringency and (t a certain extent) university regulations make the path o the wandering scholar difficult to follow.

Guy's Hospital,
London, S.E.1. PHILIP EVANS.

PREGNANCY AND RHEUMATOID ARTHRITIS

SIR,—I read with interest your annotation of Feb. 1 In 1947, Dr. Dudley Hart kindly allowed me to trea a small number of his patients with rheumatoid arthritis The constant finding of anæmia, plus the knowledge tha pregnancy caused temporary remission of symptoms suggested a deficiency in non-pregnant subjects o "substance x," present in healthy blood and necessar for the proper nutrition of joint tissues.

A system was devised whereby the patient received transfusion of fresh heparinised blood from a young adul of either sex at monthly intervals. The rapidity of thi process simulated a direct transfusion. Unfortunatel it was not possible to continue with the series of cases but it was found that patients experienced symptomati improvement, and that the erythrocyte-sedimentation rate (E.S.R.) frequently returned to near normal a few days after transfusion. The E.S.R. rose again after thre or four weeks.

It is possible that this was a non-specific effect tha had nothing to do with rheumatoid arthritis, but transfusion with ordinary stored blood did not have this effect. If this is so, then the search for this "substance x" need not be concentrated on the pregnant state as you suggest in your annotation.

Richmond, Yorkshire. K. C. EASTON.

THE HENGROVE EXPERIMENT

SIR,—Attention has often been drawn to deficiencies in the organisation of general practice in this country, but few have tried to effect improvement by reorganising the general practitioner's work. Dr. Cook deserves recognition for being one of these few, and it is with regret that we find ourselves quite opposed to the principle of his experiment of a pædiatric general practice described in his article last week.

We have previously expressed the view that "primarily the interest of the G.P. is the whole person integrated in the social background."[1] The social background of a child is above all the family; a knowledge of the family is essential to a full understanding of most medical problems of children, and a rearrangement of the relationships within the family is often the chief treatment. This may only be possible if the parents themselves are given treatment approaching to psychotherapy, which a G.P. who confines himself to children is unable to undertake; he must be very handicapped in tackling the recurring problem of the emotionally disturbed child, and also in dealing with many other conditions, including asthma and malnutrition, for which Dr. Cook holds special sessions.

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[1] *Lancet*, 1951, i, 1226.

It is our view that to raise the standards of general practice in this country it is necessary to organise groups of G.P.s working in coöperation in properly equipped health centres; but we believe it is essential that each G.P. be a family doctor with his own list of patients for whom he accepts undivided responsibility. One family should not be divided between different G.P.s because of the different ages of its members. We would urge doctors who want to take practical steps to improve general practice, themselves to organise group practices and to take an active part in the campaign for health centres.

L. M. Franklin
J. D. Paulett
R. Tepper
St. Paul's Cray, Kent. E. Tuckman.

ACUTE INFECTIONS OF THE FINGERS

Sir,—The importance of this subject possibly justifies further comment on the correspondence already published. Professor Pilcher, in your last issue, talks of my quotation of 18·7 days from Mr. Bailey's article as "an unfortunate slip." In quoting some published results, I was not concerned to make competitive comparisons, and took care to make it plain that the figures were not strictly comparable. Thus I said that Anderson's 15·8 days were from first attendance, that Loudon's 11 days were from surgical treatment, and that "Mr. Bailey gives an average of 18·7 days for disability." It is a fact that in your issue of Jan. 26 (p. 169 in table I), "Average days of disability," Mr. Bailey gives 18·7 days as "the length of disability" for pulp abscesses treated. Whether I quoted this disability time or the shorter treatment time, it was manifest that Mr. Bailey's was the most impressive series as it covered the work of a department for the whole year. I cannot see that it needed any defence.

May I suggest that one of the most important inferences to be drawn from these figures is that there has been a remarkable improvement in recent years in the results obtained for infected fingers in casualty departments up and down the country. These results have been obtained by the more widespread use of methods which have been long established. As a result casualty departments are now able to concentrate more on improving their standard of primary finger repairs. In this primary reparative work the teaching of established plastic techniques plays a major part. The treatment of hand infections is an important, but certainly not the major, aspect of the work of comprehensive hand clinics today.

Professor Pilcher asks whether I would recommend the treatment of whitlows by excision and primary suture for general use. If the published results and my own were to continue to show advantages in the method I would recommend its general adoption in casualty departments (where the majority of pulp-space abscesses are treated, and best treated). I agree entirely about the value of digital ring blocks permitting one doctor to give complete and thorough operative treatment for these cases. This is of importance both in avoiding hurried slipshod work at busy hours in casualty departments, and in allowing a single practitioner to undertake the treatment in his surgery. In over one thousand ring blocks in distal finger infections, and over five thousand in the primary treatment of finger injuries, we have seen no complications, ischæmic or infective.

London, W.1. Patrick Clarkson.

Medicine and the Law

Bruises on Children

Parents of children with purpura are sometimes unfairly suspected by their neighbours of cruel behaviour. In a Yorkshire case reported to us by the National Society for the Prevention of Cruelty to Children, a stepmother of 21, about to bear a child of her own, was believed to be ill-using her two stepsons, aged 2 and 3 years. An inspector from the society, on his first visit, shared this impression, for the children were badly bruised about the face, arms, legs, and body. The eldest, in particular, had abrasions on his neck, cheek, and left eyelid, which was much puffed up. The father explained that the children had seen a specialist, who attributed their troubles to a blood condition. Neighbours said they had heard the children screaming from time to time, and had noticed fresh marks and bruises appearing, but nobody had ever seen either of the children struck, or had seen them injured in any accidents which might have caused the bruises. The inspector visited the children's doctor, and the specialist to whom they had been sent; blood examination had not revealed evidence of purpura. Both doctors felt confident that the bruises had not been caused by violence: the children, they said, could never have stood up to the punishment the marks suggested, and moreover their relations with their stepmother seemed to be good.

At the inspector's suggestion, both children were admitted to hospital for observation; and while they were there fresh bruises appeared. This exonerated the young stepmother, who had suffered a good deal from the suspicions of her neighbours. Finally a dermatologist diagnosed the condition from which the children were suffering as epidermolysis bullosa.

The case illustrates the hardship to parents wrongfully suspected of cruelty, but also reminds us of the difficult position of their neighbours. If they ignore signs of trauma in children they may be failing in a quite obvious duty. On the other hand, if they interfere they may be doing the parents a wrong. Their proper course is to inform the N.S.P.C.C. as soon as their suspicions are aroused, and leave it to the society's inspector to set adequate inquiries on foot. Acting on his experience, and with an open mind, he will be able, like the inspector in this case, to get at the truth.

Public Health

Variola Minor in Lancashire

Up to and including Feb. 22, 40 confirmed cases of variola minor had been reported from Rochdale (38 cases) and the adjoining town of Milnrow (2 cases). Of these 40 patients, 23 have fallen ill during February, and in 17 the illness has been diagnosed retrospectively. All medical officers of health will by now have received a letter from the chief medical officer, Ministry of Health, advising them of the presence of this disease in South-East Lancashire.

Vital Statistics for Sweden

According to the Swedish Central Bureau of Statistics, the death-rate in 1948 was 9·83 per 1000 population—the lowest rate ever recorded in that country. The percentage of people aged 15–65 was 67·1, compared with 70·2 in 1940; while the percentage of children had risen from 20·4 to 22·8, and that of people over 65 years of age from 9·4 to 10. The number of births per 1000 married women aged 15–45 was 125·5 in 1948, compared with 134·7 in the years 1941–45.

Infectious Diseases in 1951.—In 1951 Sweden, with a population of just over 7 million, had 14,673 cases of notifiable infectious disease, compared with 37,287 in 1950. The number of cases of paralytic poliomyelitis, which was 1843 in 1949 and 1164 in 1950, dropped to

339 in 1951. Cases of scarlet fever numbered 13,661, compared with 34,863 in 1950. Diphtheria notifications totalled 30, typhoid fever 20, paratyphoid fever 140, dysentery 102, and meningococcal meningitis 46.

Obituary

CHARLES DANIEL PARFITT

M.D. Toronto, M.R.C.S.

Dr. C. D. Parfitt, who died last November at the age of 79, had taken a prominent part in the fight against tuberculosis in Canada.

On his father's side he came from a Somerset family, but he was born in London, Ontario. After graduating M.D. at the University of Toronto at the age of 22, he came to this country to continue his studies at St. Bartholomew's Hospital, and these years of postgraduate study gave him a lasting respect for British medicine. In 1896 he took the English Conjoint diploma, and the next two years he spent with Osler, at Johns Hopkins University, Baltimore.

This association with Osler was the paramount influence in his medical life, for Osler gave him his first opportunity to study tuberculosis intensively. In his Osler oration to the Canadian Medical Association in 1942, Parfitt, speaking of the medical school of Johns Hopkins, said: "Other members of the staff and an occasional student . . . had fallen out because of tuberculosis, and these breakdowns had become a grave matter of concern to the heads of the hospital." Among Osler's pupils who contracted the disease were Lawrason Brown and John Bruce MacCallum, and the same fate was in store for Parfitt himself. Soon after he set up in general practice in Toronto he fell ill; but after months spent in sanatoria he conquered the infection, though he was left with a damaged left lung.

This illness settled what Parfitt's life work was to be. After he had worked for some years in the sanatorium in Murkoka, ex-patients and friends built and equipped a private sanatorium, the Calydor Sanatorium, on the banks of the lake at Gravenhurst, and gave him a controlling position in running it. Here he had many years of active, happy, and successful work, not only restoring the tuberculous to health and capacity for a normal existence, but training specialists who carried his work through Canada and the United States. He also served on Canadian government commissions in tuberculosis. When he retired from Calydor Sanatorium at the age of 61 he again set up in private practice in Toronto. But he soon was appointed to the Loomis Sanatorium in the United States. After some years in this position he finally retired from active medical work to Toronto.

A friend and ex-patient writes:

"To Parfitt tuberculosis was not an affair of the lungs only. Any patient in his hands was overhauled from the hair of his head to the soles of his feet for manifestations of the disease. His knowledge of general medicine was encyclopædic and he kept in touch with the advances in medicine, not only in his specialty, but in the whole of medicine, and many of his friends and patients benefited from his knowledge of out-of-the-way diseases. Long after he retired from practice he was able to set on their feet again people who had been incapacitated for years. In his work on tuberculosis he was on to any advance in methods of diagnosis and cure like a shot. Stereoscopic X-ray skiagrams of the chest he used as early as 1917, and the later developments of lung collapse and thoracoplasty he welcomed enthusiastically. Any gadget, however small, that would help him in his work aroused his interest. For instance, he saw one of his assistants using a slide-rule in calculating Arneth counts. So he promptly learnt to use it too, and this stood him in good stead when the Canadian government commission on tuberculosis asked him at 24 hours' notice to reduce the statistics he had prepared for them to percentages. He also used the slide-rule to aid his duck shooting on a holiday in Manitoba, achieving by this mea the best bag, day after day, among his fellow sportsmen.

"He had an intense interest in life and people, in learnin and in general culture. He adored books of reference and goo literature equally. He was shrewd in judgment and could s through any situation he was confronted with, but despite his shrewdness he had a loving compassion for the foibles and failings of human beings. Oddly enough he considered hims forbidding—the last thing that he was, for he had gre charm and a courtesy which came from the heart."

Diary of the Week

MARCH 2 TO 8

Monday, 3rd

MEDICAL SOCIETY OF LONDON, 11, Chandos Street, W.1
8.30 P.M. Mr. R. C. Brock: Surgery of the Heart and Grea Vessels. (Last of three Lettsomian lectures.)
INSTITUTE OF NEUROLOGY, National Hospital, Queen Square, W.C.
5 P.M. Dr. Raymond Garcin: *Neurological manifestations o porphyrinuria.*

Tuesday, 4th

BRITISH POSTGRADUATE MEDICAL FEDERATION
5.30 P.M. (London School of Hygiene, Keppel Street, W.C.1.) Dr. O. G. Edholm: *The Effects of Hæmorrhage on th* Peripheral Circulation in Man.
CHADWICK PUBLIC LECTURE
5.30 P.M. (Westminster Medical School, Horseferry Road, S.W.1.) *Lieut.-Colonel E. F. W. Mackenzie: Prevention of Dental* Caries by the Administration of Fluorine in Public Water-supplies.
INSTITUTE OF DERMATOLOGY, St. John's Hospital, Lisle Street, W.C.2
5.30 P.M. Dr. F. R. Bettley: Antibiotics in Skin Diseases.
WEST END HOSPITAL FOR NERVOUS DISEASES, 40, Marylebone Lane, W.1
5.30 P.M. Dr. Gerald Parsons-Smith: Neurology demonstration.

Wednesday, 5th

UNIVERSITY OF OXFORD
5 P.M. (Radcliffe Infirmary.) Dr. F. M. R. Walshe, F.R.S.: Old and New Views on Localisation of Function in the Cerebral Cortex. (Litchfield lecture.)
INSTITUTE OF DERMATOLOGY
5.30 P.M. Dr. J. O. Oliver: Chemistry and Bacteriology of Antibiotics.
MEDICO-CHIRURGICAL SOCIETY OF EDINBURGH
8.30 P.M. (Royal College of Surgeons, 18, Nicolson Street, Edinburgh.) Mr. A. J. Slessor: *Peripheral and Coronary Arterial Disease.*

Thursday, 6th

UNIVER [illegible] W.C
5 P.M [illegible]
ROYAL [illegible]
5.30 [illegible]
Œsophagus.
BRITISH POSTGRADUATE MEDICAL FEDERATION
5.30 P.M. (London School of Hygiene.) Prof. G. P. Crowden: *Environmental Factors in Work.*
INSTITUTE OF DERMATOLOGY
5.30 P.M. Dr. Henry Haber: *Histopathology of Ectodermal and Mesodermal Nævi.*
INSTITUTE OF CHILD HEALTH, *Hospital for Sick Children, Great* Ormond Street, W.C.1
5 P.M. Mr. H. J. Seddon: Modern Orthopædic Principles.
ST. GEORGE'S HOSPITAL MEDICAL SCHOOL, Hyde Park Corner, S.W.1
4.30 P.M. Dr. D. J. Williams: Neurology lecture-demonstration.
LIVERPOOL MEDICAL INSTITUTION AND MANCHESTER MEDICAL SOCIETY
4.30 P.M. (114, Mount Pleasant, Liverpool, 3.) Prof. Robert Platt: Opportunities for Research in General Practice. Prof. W. F. Gaisford: Art in Pædiatrics.
UNIVERSITY OF ST. ANDREWS
5 P.M. (Medical School, Small's Wynd, Dundee.) Dr. A. G Anderson: *Problems Connected with Old Age.*

Friday, 7th

UNIVERSITY COLLEGE, Gower Street, W.C.1
5.30 P.M. Prof. J. F. Danielli, D.SC.: Cell Physiology and Pharmacology.
INSTITUTE OF DERMATOLOGY
5.30 P.M. Dr. R. T. Brain: Common Skin Diseases in Childre
INSTITUTE OF DISEASES OF THE CHEST AND INSTITUTE OF CAR-DIOLOGY
5.30 P.M. *(London School of Hygiene.) Dr. Graham Hayward:* Rheumatic Heart-disease.

EMERGENCY BED SERVICE.—In the week ended la Monday applications for general acute cases numbered 113 The proportion admitted was 88·8%.

Notes and News

INSECTICIDES

ST month a working party convened by the Economic Social Council of the United Nations estimated that D.D.T. made in the major producing countries in 1951 nted to about 59,000 metric tons, while in 1952 produc- would total about 77,000 metric tons. There is thought resent to be no significant shortage in the world of either T. or B.H.C.

troducing a series of papers at the Royal Society of ical Medicine and Hygiene on Feb. 21, Prof. P. A. TON, F.R.S., gave some fascinating and little-known ils of the introduction of small amounts of D.D.T. into land and the United States, from Switzerland, during 1942, when the supplies of pyrethrum to the Allies were tly depleted by Japanese conquests and by two adverse sons in Kenya. The investigation and exploitation of .T. and its manufacture on a large scale within the next months, in which he and his colleagues and entomologists the United States were active, were of great importance he war effort.

he modern insecticides have revolutionised methods of trolling many of the great killing diseases of man and mals. Their effects on health have been greater than those the chemotherapeutic agents in that the insecticides have only reduced the number of deaths, but have, by their in agriculture, made possible the production of more d to keep from famine those who without them would e died from disease. Professor Buxton showed that in early investigations much work was done in ignorance n of the questions to be answered, and went on to argue need for exact laboratory work, especially in relation to phenomenon of resistance.

Prof. G. MACDONALD elaborated a mathematical assessment the various factors which influence the transmission of sease, taking malaria as the example. In this work r. Macdonald is very fittingly continuing the work done many ars ago by his predecessor at the Ross Institute, Sir Ronald oss.

Mr. A. B. HADAWAY, PH.D., and Mr. F. BARLOW dealt with ysical factors affecting the efficiency of insecticides—the rosols and sprays, solvents, emulsions, and wettable powders -and the surfaces on which they are deposited. Differences tween certain of their results and those obtained in Kenya, entioned by Mr. G. DAVIDSON, could probably be explained y the fact that they were working with walls of ground ud whereas Mr. Davidson was working with surfaces of ud and stone; and these differences obviously affect bsorption of insecticides. Mr. Davidson observed a lethal ffect of 'Dieldrin' on mosquitoes kept in cages away from he sprayed walls, although dieldrin has no fumigant effect; nd Dr. Hadaway suggested that this might be explained y scattering into the air of minute particles of the insecticide hen the floor of the hut was swept.

Mr. J. R. BUSVINE, D.SC., discussed the newer insecticides relation to insects of medical importance; this aspect is ound up with resistance, which, so far as the chlorinated ompounds are concerned, is related to the ability of flies break off chlorine and to render the compound non- xic. Mr. P. BRACEY described his process of incorporating e insecticide in urea-formaldehyde resin in the form of solid solutions" in which the insecticide blooms on to the urface even after being wiped off.

Miss MARY HARRISON, PH.D., remarked that in house-flies esistance to the chlorinated compounds is common enough; ut no case of resistance to 'Parathion' or the phosphorous ompound has been reported, though some flies have been found esistant to pyrethrum.

The toxicity of insecticides to mammals was dealt with y Dr. J. M. Barnes, who referred particularly to experimental ork on D.D.T., B.H.C., 'Chlordane,' 'Aldrin,' and dieldrin. he chlorinated hydrocarbons can act as convulsive poisons, nd produce visible changes in the liver and sometimes in ther tissues; but, as Professor Buxton remarked, on the hole they are remarkably free from danger in ordinary se. Barbiturates can control the convulsions to which eavy doses of these substances give rise; but barbiturates re not antidotes.

In the final paper Mr. R. C. MUIRHEAD-THOMSON, D.SC., rof. R. M. GORDON, and Prof. T. H. DAVEY set out what many people appeared to think a formidable list of factors to be taken into consideration in planning experiments on insecticides.

NATIONAL REGISTRATION NUMBERS

ALTHOUGH identity cards have been abolished, National Registration numbers will still be used in the National Health Service. Numbering is necessary to identify patients and to avoid inflation of doctors' lists; and to save the labour and expense of allotting new numbers the old National Registration numbers will be kept for this purpose. The Ministry of Health, therefore, reminds us all that before we throw away our identity cards we should make sure that our National Registration numbers are on our medical cards. The numbers will in future be known as National Health Service numbers, and registrars of births will issue a preliminary medical card and a N.H.S. number for babies. Doctors are asked to obtain the N.H.S. number of any new patients and to quote the number when required—e.g., on maternity and temporary-resident forms. If a patient has only lately arrived in this country and has no number, his normal residence should be entered on his form instead.

A NEW FIELD DRESSING

THE Surgeon-General to the U.S. Army has described [1] a new field dressing which has been successfully used in Korea. The dressing was originally designed for the first-aid treatment of people burned in an atomic explosion, but it has proved so valuable for large and multiple wounds that its name has been changed to "universal protective dressing." It consists of a single pad, 22 in. wide, in which 1/2 in. of absorbent cotton is covered by fifteen sheets of cellulose paper and an outer layer of a tough paper known as 'Masland.'

University of Oxford

Magdalen College has appointed Prof. C. J. Singer to a fellowship by special election.

University of Leeds

Dr. I. M. P. Dawson has been appointed lecturer in pathology, and Dr. C. O. Carter medical geneticist.

The trustees of the Anna Fuller Fund of New Haven, Connecticut, have given £100 to the university in memory of King George VI. The money is to go towards the cost of the electron microscope recently installed in the department of experimental pathology and cancer research.

University of Sheffield

The council has established a separate department of microbiology and has appointed Mr. S. R. Elsden, PH.D., senior lecturer in microbiology, to be in charge of the new department.

University of Edinburgh

On Feb. 19, Sir Alexander Fleming, F.R.S., was installed as rector.

Royal College of Physicians of London

On Tuesday and Thursday, March 11 and 13, Prof. John McMichael will give the Oliver-Sharpey lectures on the Dynamics of Heart-failure. On Tuesday and Thursday, April 1 and 3, Prof. Robert Platt will give the Lumleian lectures on Structural and Functional Adaptation in Renal Failure. All the lectures will be held at 5 P.M. at the College, Pall Mall East, S.W.1.

Chesterfield Medal

The examination for the Chesterfield medal in dermatology will be held at the Institute of Dermatology, St. John's Hospital for Diseases of the Skin, Leicester Square, London, W.C.2, on Monday, Tuesday, and Wednesday, April 7, 8, and 9. Particulars may be had from the secretary of the institute.

British Council Surveys

Among the specialist surveys for overseas visitors to be held this year by the British Council, are the following: anæsthesia (London), March 9–21; diet in health and disease (Aberdeen, Edinburgh, and Glasgow), May 18–31; engineering aspects of public health (London, Birmingham, and Manchester), June 29–July 12; industrial medicine in Great Britain (Manchester and Birmingham), Sept. 18–Oct. 7; and recent advances in internal medicine (London and Oxford), Nov. 2–15.

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[1] *New York Times*, Feb. 18, 1952.

Technique of Medical Teaching

A conference course on this subject is to be held at the London School of Hygiene, Keppel Street, W.C.1, on Friday and Saturday, March 28 and 29. Further particulars will be found in our advertisement columns.

Tuberculosis Essay Prize

The National Association for the Prevention of Tuberculosis offers a prize of 100 guineas for an essay on the control of tuberculosis by a public-health medical officer. Further particulars can be had from the secretary-general, N.A.P.T. Tavistock House North, Tavistock Square, London, W.C.1.

Association of Workers for Maladjusted Children

The annual general meeting of the association will be held in the rooms of the National Association for Mental Health, 39, Queen Anne Street, London, W.1, on Saturday, March 15, at 11 A.M. At 2 P.M. Mr. David Wills will open a discussion on the training of workers with maladjusted children.

C.M.F./M.E.F. Dinner

The C.M.F./M.E.F. *Physicians' seventh reunion dinner* will be held at Grosvenor House, London, W.1, on Saturday, April 5, with Dr. E. R. Boland in the chair. Further information may be had from Dr. A. Willcox, 66, Harley Street, London, W.1.

Malaria Control in the Philippines

On Feb. 16 a World Health Organisation team, led by *Dr. G. Sambasivan, began residual spraying in the Island of* Mindoro, about 100 miles south of Manila. It is hoped that protection against malaria will be extended to more than 50,000 people within eighteen months, when government teams will take over the project from the W.H.O. group.

St. John Ambulance Brigade

The Northern Surgeons' Conference of the brigade will be held at the Spa Hotel, Buxton, on Saturday and Sunday, April 26 and 27. Sir Harry Platt, Mr. R. Guy Pulvertaft, and Major Harold Stewart will speak. Further information can be *had from the conference secretary, St. John Ambulance* Brigade, 8, Grosvenor Crescent, London, S.W.1.

Advisory Council on Alcoholism

This council has been brought into being, under the chairmanship *of Dr. T. A. Munro, with the primary aim of arousing* public awareness of the problem of alcoholism. Information centres are to be established in London and elsewhere. The hon. secretary is Mr. Forbes Cheston, 99, South Hill Park, London, N.W.3.

Employment of Older Men and Women

The Minister of Labour and National Service has set up a national advisory committee to advise him how to promote the employment of older men and women. The chairman is to be Sir Peter Bennett, parliamentary secretary to the Ministry, and the committee will include representatives of the Ministry of Health and the Department of Health for Scotland. The interests of local authorities, of medicine, research, and social science, and of welfare organisations will also be represented.

Congress of Military Medicine

The 14th International Congress of Military Medicine and Pharmacy will be held in Montevideo, Uruguay, from March 1 to 6, 1953. The main subjects chosen for discussion are: Military Medicine as a Specialty; National Medical Organisation in War; Sanitary Services in War; First-aid Treatment of Burns and Wounds. Further information may be had from Dirección General del Servicio de Sanidad Militar, Avda. 8 de Octubre y Mariano Moreno, Montevideo, Uruguay.

National Corporation for Old People

During 1950–51 the corporation has given over £150,000 to voluntary committees to be used for the benefit of old people. During the four years of its existence the corporation has made grants to 150 homes which accommodate nearly 3000 old people. To show the need for an intermediate home between the hospital and the homes provided by the local authorities, the corporation has used funds provided by the people of South Africa to purchase and adapt two large houses, one near Belfast and one at Stanmore, Middlesex. When open, these link homes will work in close conjunction with hospitals.

Blood-transfusion Conference

A conference of medical and other workers on blood-tr fusion is to meet at the British *Standards Institution*, Victoria Street, London, S.W.1, from March 3 to 5, to the international standardisation of blood-transfusion eq ment. The conference is being held under the auspices of International Organisation for Standardisation, and nations are sending delegates. Observers have been invi from the League of Red Cross Societies, the Internatic Blood Transfusion Society, the Permanent Internatic Commission for the Study of Medical Equipment, and World Health Organisation. The chair will be taken by Alan Drury, F.R.S.

Prof. Dorothy Russell, director of the Bernhard Baron Instit of Pathology at the London Hospital, is lecturing for the Bri Council in Malta between Feb. 27 and March 8.

Dr. Brock Chisholm, director-gener [illegible] sation, left Geneva on Feb. 12 for a [illegible] India, Ceylon, Singapore, Thailand, [illegible] Japan, Canada, the U.S.A., and Er [illegible] *Geneva on April 25, Dr. Chisholm will attend the Health Cong* of the Royal Sanitary Institute at Margate on April 22 and 23, will give an address at London University on April 24. During absence from Geneva his place is being taken by Dr. Pierre Doro deputy director-general.

Appointments

BROOKS, D. M., M.A., M.B. N.U.I., F.R.C.S.I.: consultant surge [illegible] rehabilitation departments, Royal Natio [illegible] London.

CONY[illegible], R. M., [illegible]: factory doctor, Lasswade distri Midlothian.

GROSS, *DÉSIRÉE*, *M.D. Leeds*, D.P.H.: *deputy M.O.H. for Ilford*, a asst. county M.O.H. for Essex.

PARKINSON, T. J., M.B. St. And., D.C.H.: medical registrar, Sou mead Hospital, Bristol.

STEWART, AUDREY, M.B. Manc., D.OBST.: asst. M.O.H. for matern and child welfare, *Portsmouth Public Health Department.*

East-Anglian Regional Hospital Board:

BARLOW, K. E., M.R.C.S., F.F.R.: consultant radiologist, E Suffolk and Ipswich area.

DENNESS, THOMAS, M.B. Lond., M.CH.ORTH. Lpool, F.R.C. consultant orthopædic surgeon, East Suffolk and Ipswi area.

PUGH, A. M., M.B. Glasg., D.T.M. & H.: [illegible] hospitals [illegible]

SHOENBERG, [illegible] psychiatry, [illegible]

Liverpool Regional Hospital Board:

FALK, SAMUEL, M.D. Manc., D.P.M.: consultant psychiatri Rainhill Hospital.

HELLER, G. C., M.D. Prague: asst. psychiatrist, Rainhill Hospit

O'FLANAGAN, P. M., L.R.C.P.I., D.P.M.: asst. psychiatrist, Winwi Hospital.

TASKER, R. G., M.A., M.B. Camb.: asst. pathologist, hospitals the Ormskirk area.

WADDINGTON, J. K. B., M.B. Lpool, F.R.C.S.E.: consulta surgeon, regional thoracic unit.

WODZINSKI, A. J. J., M.D. Cracow: asst. pathologist, Walt Hospital.

The Terms and Conditions of Service of Hospital Medical a Dental Staff apply to all N.H.S. hospital posts we advertise, unl otherwise stated. Canvassing disqualifies, but candidates may normal visit the hospital by appointment.

Births, Marriages, and Deaths

BIRTHS

ELLIOTT.—On Feb. 24, at Crowborough, the wife of Dr. Jo Elliott, G.M.—a son.

HICKS.—On Feb. 16, at *Hove, the wife of Dr. S. Leighton Hic* —*a son.*

JAMES.—On Feb. 19, at Stanborough, the wife of Dr. J. D. Jam —a son.

ORFORD SMITH.—On Feb. 15, in Birmingham, the wife of Dr. E. S Orford Smith—a daughter.

PILSWORTH.—On Feb. 15, in London, the wife of Dr. W. L. *Pilsworth*—a son.

WEBB.—On Feb. 15, in London, the wife of Dr. Hughie Webb— a son.

DEATHS

ARMSTRONG.—On Feb. 19, at Braintree, Essex, John Thoma Armstrong, L.R.C.P.E.

CAMPBELL.—On Feb. 16, John Alexander Langford Campbell, O.B.E. M.D. Lond., surgeon-captain, R.N. retd.

DAVIES.—On Feb. 20, at Towyn, Merioneth, John Alban Davie L.M.S.S.A.

HOBBS.—On Feb. 21, at Caterham, John Hobbs, L.R.C.S.I., late major, R.A.M.C., aged 89.

LECKIE.—On Feb. 18, at Perth, Joseph Primrose Leckie, M.B. Edin F.R.C.P.E.

WELLS.—On Feb. 17, at Roydon, John Edmund Bishop Well M.R.C.S., major, R.A.M.C., T.F. retd.

NTERIOR CINGULECTOMY IN THE REATMENT OF MENTAL DISEASE

C. W. M. Whitty
D.M. Oxfd, M.R.C.P.

J. E. Duffield
D.M. Oxfd, D.P.M.

P. M. Tow
M.B., Ph.D. Lond.

Sir Hugh Cairns
D.M. Oxfd, F.R.C.S.

Departments of Medical and Surgical Neurology, Radcliffe Infirmary, and Littlemore Mental Hospital, Oxford

the surgical treatment of mental disease there have several recent attempts to find an effective operation h is limited in extent and anatomically precise. In paper we report the results of bilateral removal of the rior half of the cingular gyrus (fig. 1).

he limited operations have been introduced because standard frontal leucotomy lacks anatomical precision its effects are not wholly satisfactory. Although the ıdard operation often relieves or reduces the patient's ıtal distress and may improve some aspects of his aviour, it may also damage his personality.[1] In anced psychosis these unwelcome effects may be a ondary consideration, but in the treatment of psychocal illness in sane persons any reduction in the ıdards of conduct will tend to mar the result.

he more limited operations include frontal topectomy ttler et al. 1949), undercutting of limited areas of the ıtal cortex under direct vision (Scoville 1949), and trocoagulation of limited areas of the thalamic lei (Spiegel and Wycis 1949). Clinical benefit, with change of personality than with frontal leucotomy, been claimed for each of these procedures, but none so far shown such obvious advantages as to take the ld against all others.

Though our choice of the anterior cingular gyrus ea 24 of Brodmann; fig. 1) was based mainly on ysiological considerations, two clinical observations o seemed relevant. Firstly, Freeman and Watts 44) had noted that the confusion and loss of tension n immediately after standard leucotomy seemed to low section of some relatively small bundle of fibres ar the cingular gyrus. However, the careful postrtem studies of Meyer and his colleagues (Meyer and Lardy 1949, Beck et al. 1950), failed to correlate ccessful results of the operation with damage of that ea, or, indeed, of any other limited region of the frontal bes; and while they did suggest that the cutting of edial, rather than lateral, fibre tracts was important, ey specifically excluded involvement of area 24 as neficial (Meyer and McLardy 1949). Secondly, the rly mental change seen in some anterior corpus callosum mours, but not with congenital absence or surgical ction of this structure, also seemed to implicate ysfunction of the cortex in the cingular region as a use of the mental symptoms. However, the clinical vidence was slight.

By contrast, animal experiments strongly suggested at area 24 played an important part in the affective pects of normal behaviour. In monkeys, stimulation f area 24 produced autonomic responses of a sort that re associated with emotion—vocalisation, dilated pupils, e erection of hair, and alterations in breathing, pulserate, and blood-pressure; and bilateral excision of the area was followed by a temporary increase of tameness and reduction of aggressiveness, with apparent loss of sense of danger (Smith 1944, 1945, Ward 1948a, Glees et al. 1950). These facts gave some support to the view, earlier elaborated by Papez (1937), that the cingular gyrus, with the hypothalamus, anterior thalamic nuclei, and hippocampus, and their interconnections, forms the neurological substrate of emotional experience and also participates in emotional expression. That these are not the only parts of the brain concerned with emotion seems probable from experiments in Fulton's laboratory and elsewhere. Fulton (1951, p. 101) has recently developed the view that "the orbito-insulo-temporocingulate complex is concerned with emotional expression, whereas lateral aspects of the neopallium are primarily concerned with learning, memory, and 'intellectual' function." Psychiatric treatment has hitherto been so largely empirical that any reasonable working hypothesis which can be subjected to therapeutic test is welcome. Hence, in July, 1948, we began to excise the anterior part of the cingular gyrus in monkeys (Glees et al. 1950) and in man.

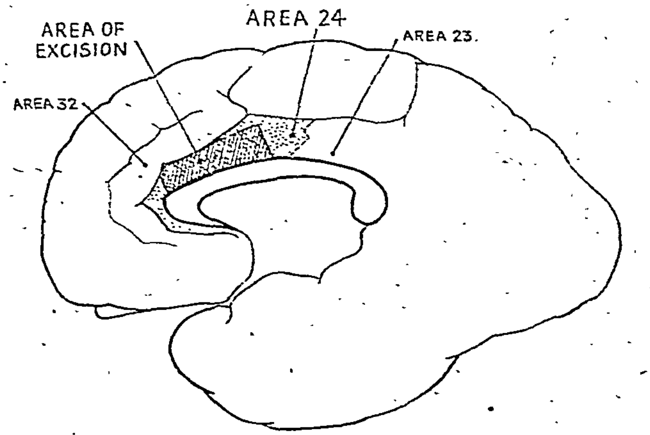

Fig. 1—Diagram of medial surface of the brain showing area of operative removal in relation to Brodmann's areas.

The cingular gyrus and adjacent areas have been undercut in man by Scoville (1949) and in one case by Ward (1948b), and Mr. R. A. Bailey of Manchester reported a somewhat similar procedure to the Society of British Neurological Surgeons in the summer of 1950. Mettler, Pool, and their colleagues (Mettler et al. 1949, case 40) reported one case of bilateral removal of most of area 24 and part of area 32; the condition of the patient, a paranoid schizophrenic, was not changed by the operation. Le Beau and Pecker (1950) have also made limited removals of the medial frontal cortex, the areas involved again being 32 as well as 24. Their cases have been ones of anxiety or aggressive outbursts, usually in a setting of epilepsy. Of the 8 reported, 5 showed some improvement in behaviour without intellectual or undesirable personality change; but the period of observation after operation was too short for final judgment. All of these operations have been more extensive than ours.[2]

The Operation
(FIGS. 1 AND 2)

In our first patient the anterior part of the cingular gyrus of the dominant hemisphere only was removed, without any change in the patient's symptoms. Three months later the corresponding area of the right side was also removed, and then the patient improved. Since that experience both areas have always been removed at the same operation. The area of extirpation corresponds to area 24 of Brodmann's map of the human cortex, but fails to remove the rostral part of area 24, probably also the caudal part, and is thus subtotal (fig. 1).

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[1] Allport (1949) defines personality as "the dynamic organization in the individual of those psychophysical systems that determine his unique adjustments to environment." Though somewhat cumbersome, and descriptive rather than definitive, this attempt is valuable because it emphasizes the reactive quality of personality, its dual substrate—physical and psychic—and its unique, individual character.

[2] Fulton (1951) mentions that Dr. Kenneth Livingston has also performed bilateral cingulectomy in 51 psychotic patients with favourable short-term results in 15.

A small right frontal osteoplastic flap is reflected, and the dura of the anteromedial angle of the flap is opened (fig. 2). The medial surface of the right frontal lobe is retracted until the white corpus callosum, with the anterior cerebral arteries lying on it, is visible. After incision of the pia-arachnoid, the anterior part of the cingular gyrus of each side is removed by suction, due care being taken to avoid damage to the anterior cerebral arteries and their branches (fig. 3).

In this series the amount of the gyrus removed measured up to 4 cm. in length (fig. 4), about 1 cm. in breadth, and 1 cm. in depth. The weight of a comparable amount of tissue removed at necropsy is about 1·5 g. per side—that is to say, a total removal of 3·0 g. This material includes white matter as well as cortex. The corpus callosum is left widely exposed in the bed of the excision, and we assume that the cingulum, which we have not been able to identify in the living unfixed brain, is also removed in part of its course. Our aim has been to destroy as much of the anterior half of the cingular gyrus as possible, and when the length of gyrus removed is for any reason greatly below 4 cm. the grey matter of the gyrus has been undercut by blunt dissection for up to 1 cm. beyond each end of the incision.

The anterior end of the excision usually lies immediately above the anterior edge of the genu of the corpus callosum. The cingular gyrus extends downwards around the genu, but as it passes ventrally it narrows and its surface is partly covered by arteries (fig. 3), with the result that its removal in this region would usually entail considerable risk of hæmorrhage from the anterior cerebral arteries or their main branches, and in a relatively inaccessible position.

Three phases of this operation call for further comment: the division of cerebral veins, the separation of the two hemispheres, and the identification and removal of the gyrus.

In order to retract the medial surface of the right fr lobe from the falx it was necessary in 24 out of 29 cas divide one or more venous tributaries of the sagittal s from the convex and medial surfaces of the right fro lobe. On a few occasions this interference with ve drainage set up a small subpial extravasation of blood in gyri drained. And probably it always produces some dif damage to the frontal lobe, for in monkeys Dr. Glees found considerable degeneration of white matter following division of frontal tributaries of the sagittal sinus. It is therefore desirable to limit the damage by conserving as many veins as possible.

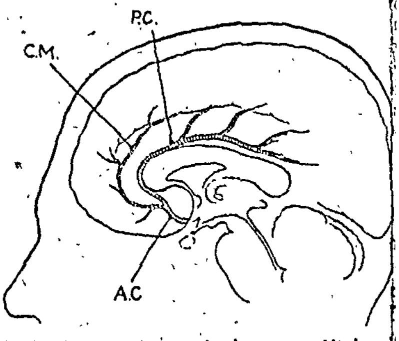

Fig. 3—The anterior cerebral artery and its branc A.C., anterior cerebral, C.M., calloso-margi P.C., pericallosal.

The separation of the medial surfaces of the frontal lo from one another below the free edge of the falx cerebri made difficult by numerous fine vascular adhesions and, places, by fusion of the leptomeninges of the two sides. W patience and gentleness these adhesions could be satisfacto divided. What was more serious was the occasional find of a large arterial branch passing from the surface of hemisphere across to the other. Retraction of the me surface of the right frontal lobe could be assisted by wi drawing cerebrospinal fluid from the right lateral ventri but this step was not usually necessary. In one case, included in this series, the falx cerebri was absent and medial surfaces of the frontal lobes were so densely insepara that the operation had to be abandoned in favour of orbital undercut.

The identification of the cingular gyrus depends on expos of the corpus callosum, which from the whiteness of its sur looks quite different f any of the surround tissues. We did not ap ciate this point at fi and on at least occasions, misled finding the main pa anterior cerebral art in the normal posi of the calloso-marg arteries (fig. 3), we moved the lower par the superior frontal g (area 32) in mistake for anterior part of the cingu gyrus (area 24). There so many variations in position and size of anterior cerebral art that these vessels are reliable guides to position of the cing gyrus.

The unilateral frontal approach us exposed both cing gyri, but in 3 of 29 it was necessary to d the lower free margi the falx to display whole of the left cin gyrus.

The cingular gyri o site of removal are us crossed at one or places by branches o calloso-marginal or callosal arteries. In desire to confine our lo

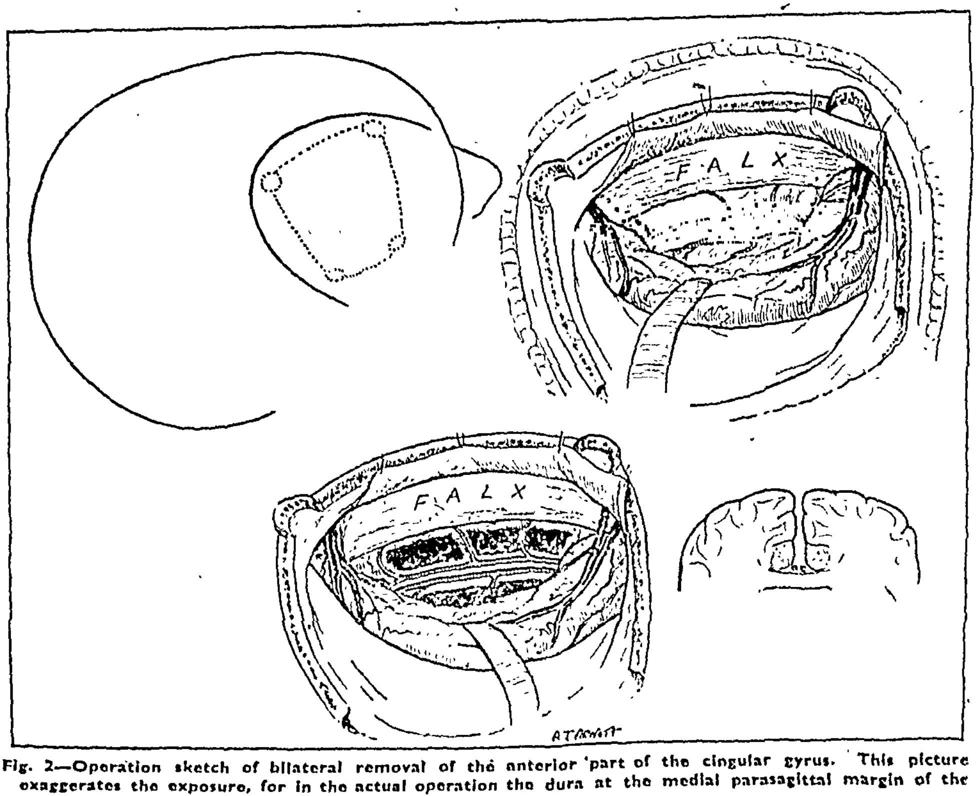

Fig. 2—Operation sketch of bilateral removal of the anterior part of the cingular gyrus. This picture exaggerates the exposure, for in the actual operation the dura at the medial parasagittal margin of the flap is opened only in its anterior half.

losely as possible to the anterior part of the gyri we have ght to conserve these arterial branches and have been essful in all but 2 cases. Consequently it has been essary to remove the brain tissue by means of a fine-ited sucker, and often to leave small bridges of brain ue beneath the arterial branches (fig. 2). In the 2 excep-ial cases there was bleeding from one calloso-marginal ery which had to be stopped by diathermy; no unusual nptoms were observed after operation in these cases. In case the frontal sinuses were so large that to avoid them osteoplastic flap was more posteriorly placed than usual, l the cingular excision probably encroached on the posterior t of the gyrus (area 23); no unusual effects were served.

Observations During and Immediately After Operation

Physiological.—In one patient we were able to operate der local anæsthesia. One or other cingular gyrus is stimulated with pulses of 0·02 milliseconds, 2·5 volts, d 10 to 100 cycles per second, without any obvious ects. During this stimulation and during the sub-quent removal of area 24 the patient could talk freely d use his limbs, he could calculate and answer questions telligently, and he was not aware of any change in his notional or physical state. In the other patients, erated on under general anæsthesia, application of athermy to one cingular gyrus was followed on few occasions by a deep sighing breath or fall pulse-rate, but for the most part no change was served.

In the first days after operation no change in the ysiological state of the patients was usually observed; particular, no weakness or paralysis of limbs, and disturbance of speech. No generalised motor restless-ss was noted. In some patients, however, small, petitive, seemingly purposeless movements, such as tting the bedclothes or rubbing the face, occurred for time. In one, a tic-like sniff developed. These were miniscent of the behaviour commonly seen early after lateral frontal-lobe wounds. A few patients were nporarily incontinent, and a few had fits in the first eek after operation (vide infra). In 3 cases there was unusual amount of vomiting in the first forty-eight ours, and in 2 there was hiccup for a few days. One tient had glycosuria on the fourth day after operation, d in the ensuing two days was indiscriminately amorous. no patient who could be tested was there any alteration sense of smell after excision of the gyri.

Psychological.—As described above, one patient under al anæsthesia felt quite normal and behaved in a tional and fully orientated fashion while his cingular ri were being removed. In the first days after operation ere was no striking change in the psychological state. e obsessions and hallucinations persisted, but there emed to be a lessening of tension in most of them ich was progressive for a few days. Some of this early provement may have been due to the novelty of being a surgical ward and receiving the close attention en to patients at the time of an operation, or even the relief at surviving the operation. Three patients display some evidence of confusion in the first days er operation, particularly in their temporal orientation. we did not search carefully for this in all patients, propose to defer discussion on this point until ther observations have been made. The significance the findings so far available is not at present ar.

he Operative Risk.—This operation has been done on patients between July, 1948, and August, 1951. e patient, a woman of 56 with mitral stenosis, died ee months after operation, which had failed to relieve rolonged and severe involutional melancholia. After electrically induced convulsion three weeks after ration she developed a mild meningitis, and a small ection of pus (gram-positive cocci on films only) was found in the bed of the cingular ablation. This infection was cleared up by aspiration and by instillation of penicillin, but the patient remained demented, developed bronchopneumonia, and died.

Material and Results

Assessment of the results soon after operation has proved misleading, indicating sometimes a worse and sometimes a better result than was verified by subsequent experience. Consequently we shall consider only those 24 patients who have been observed for one and a half to three years since operation (tables I and II). There were 10 men and 14 women, and their ages varied from 20 to 68. Of these, 16 had long-standing illness and most showed considerable deterioration of personality: 13 were chronic psychotics, 2 were mental defectives, and 1 had a post-encephalitic behaviour disorder. All of them had had long trials of various other physical treatments such as E.C.T., insulin, and narcosis; 2 had already had leucotomy. The remaining 8 patients had well-preserved basic personalities either with severe disabling psychoneurosis or with a mild psychosis which had not yet encroached much on the personality; all of these had had some physical treatment, and 1 had had leucotomy.

TABLE I—16 CHRONIC CASES WITH PERSONALITY DETERIORATION

Case no.	Age and sex	Diagnosis	Length of illness (years)	Time in hospital (years)	Length of follow-up (years)	Result
	33 M	Postencephalitic behaviour disorder	22	2	3	Slight improvement (had had previous leucotomy)
1	25 M	Schizophrenia (catatonic)	9	6	3	Improvement for 4 months
3	53 F	Mental defective with aggressive outbursts	—	11	3*	Much improved for 4 months. Relapsed: leucotomy 1 year later
2	27 M	Schizophrenia (hebephrenic)	12	9	2¼	Improvement for 4 months
	54 F	Recurrent mania	12	1¾	2¼	Improvement for 3 months
	40 M	Schizophrenia (paranoid)	12	8	2¼*	Illness unaffected. Leucotomy 7 months later
	31 M	Schizophrenia (catatonic)	14	14	2¼	Slight improvement for 2 months
	45 F	Schizophrenia (paranoid)	7	7	2½	Illness unaffected. 2 years later sudden improvement (previous leucotomy)
	20 F	Mental defective with aggressive outbursts	—	2	2½	Slight improvement for 4 months
	18 F	Schizophrenia (hebephrenic)	3	2	2½	Slight improvement for 3 months
	32 F	Schizophrenia (catatonic)	4	1¼	2½*	Illness unchanged. Leucotomy 8 months later
	21 F	Schizophrenia (hebephrenic)	3	1	2½*	Illness unchanged. Leucotomy 7 months later
	42 F	Schizophrenia (hebephrenic)	21	21	2¼	Slight improvement for 2 months
	61 F	Presenile dementia with obsessional features	2	1½	2¼	Slight improvement for 1 month
	68 M	Melancholia ..	19	19	2†	Improvement for 3 months
	56 F	Melancholia ..	3	3	½†	Illness unchanged

* Follow-up includes period after further operation. † Died.

SIXTEEN CHRONIC CASES

(Table I)

The work developed broadly in two stages which are reflected in the results. The first patients were mostly deteriorated psychotics, inmates of a mental hospital, who had been ill for many years. Two of them had already had the standard leucotomy, without improvement. The schizophrenics were disorderly, deteriorated individuals, defective in personal habits; 2 were predominantly paranoid, 3 catatonic, and 4 hebephrenic. Another patient suffered from a disorder of conduct following encephalitis in childhood. In most of these patients cingulectomy was followed by improvement: destructive behaviour and sudden, unpredictable aggressive outbursts were reduced, and there seemed to be lessening of tension and obsessive concern. But there was an early relapse in most cases.

Case 1.[3]—An unmarried man of 25 had been in a mental hospital with schizophrenia for seven years. He was withdrawn and at times hallucinated. He was obsessed with hypochondriacal delusions about his head and heart. These seemed to cause him great distress. He had occasional impulsive outbursts when he would attempt to break furniture, or attack other patients, and periods when he seemed in a state of abject terror. At times he was fatuous in behaviour, with bizarre grimacings, mannerisms, and echolalia. He had shown temporary improvement with E.C.T., which he had had on 45 occasions, and once this was followed by a spontaneous fit.

Cingulectomy was performed in January, 1949. After this there was reduction in tension and anxiety, and he no longer complained of his heart or head. He attended occupational therapy regularly and worked well. He ate enormously and put on weight. At interviews the tremors, tachycardia, and dilated pupils which had been noted before operation were absent. Four months after operation, however, he again began to have impulsive outbursts and passed for a time into a catatonic stupor with waxy flexibility. He recovered from this, but remained in a fatuous and apathetic state. Two years after operation he was still apathetic and withdrawn, at times inaccessible, but less prone to impulsive behaviour, easier to manage, and at no time complaining of hypochondriacal fears, or showing somatic evidence of acute anxiety. However, he still had to be kept in the refractory ward, and from September, 1949, onwards he had three to four generalised convulsions a year.

Case 2.—An unmarried man aged 27 had been in a mental hospital for eight years with schizophrenia. He was hallucinated, noisy, restless, suddenly aggressive, and very destructive. He would tear ordinary clothing to pieces in a few hours, and had even managed to tear "strong clothing." Some improvement with leptazol ('Cardiazol') allowed a period at home. When he returned, impulsive and destructive behaviour was again conspicuous. He was temporarily and slightly improved by repeated E.C.T., which was regarded largely as sedative. But most of the time he was inaccessible, and in the year before operation he lost 9 lb. in weight.

Cingulectomy was performed in February, 1949. For the next four months he was improved. He made some contact with his environment, would converse with the staff, went to occupational therapy and the cinema. He was no longer destructive and could wear ordinary clothing, he had no impulsive outbursts, and he was moved to a better ward. His appetite became ravenous, and in the three months after operation he gained 14 lb. in weight. Gradually he relapsed. He had to be returned to strong clothing, and to the refractory ward, and became dirty and untidy. Two years after operation he remained in this state, but he was less aggressive to the staff, and his impulsive outbursts were less frequent and less violent than before operation.

In those patients in whom it was possible to judge, there seemed no evidence of the disinhibited behaviour sometimes seen after leucotomy. Moreover, as temporary improvement occurred in tension, aggressive outbursts, and obsessional features, it was decided to operate on patients who were not necessarily advanced psycho but in whom aggressive outbursts or tension and o features were pronounced.

Case 3.—A single woman aged 53 had been feeble-min from birth, but had been able to work in domestic serv She was admitted to a mental hospital at the age of 42 follo an attempt at suicide, and remained in hospital therea During this time she worked in the wards, but her cond was unpredictable, and she was given to sudden aggres outbursts. In one of these she attempted to strangle a fell patient, and therefore had to be confined to the refract ward, though she was often placid, well behaved, and a g worker.

Cingulectomy was performed in February, 1949. For next four months she was less active, talked less, had aggressive outbursts at all, and worked well. She was tr ferred to a better ward. At this time she spontaneo remarked that she did not have the sudden feelings of an which she used to have. However, angry outbursts recur At first they were only verbal, but six months after operat she tried to attack a patient with a broom and so had to sent back to the refractory ward. At this time stand leucotomy was performed without noticeable change. Eight months after, her outbursts were much less frequent and intense, but as they were still unpredictable she remained i refractory ward.

Here again some temporary improvement occurr and there was no evidence of unwanted changes personality. By this time it was also clear that in initial cases, mainly schizophrenics, improvement only temporary; indeed, 5 patients had relap sufficiently for standard leucotomy to be undertake Cingulectomy was therefore abandoned for cases show a frankly psychotic reaction.

Of the 16 chronic cases 1 died within a few months operation, 5 were unimproved, and 10 showed impro ment which was, however, for the most part transie Typically, after operation the patient was quieter a behaved more rationally, but after about four month relapsed to his former state. However, 2 patients w maintaining some degree of improvement nearly t years after operation, though there was no indication any substantial recovery. Another patient began show marked improvement two years after cingulecto

TABLE II—8 CASES WITH WELL-PRESERVED PERSONALIT

Case no.	Age and sex	Diagnosis	Length of illness (years)	Time in hospital (years)	Length of follow-up (years)	Result
	27 F	Obsessive-compulsive neurosis	12	8	$2\frac{3}{4}$	Much improved but result of operatio (Previous leucotom
4	38 F	Obsessional neurosis	23	2	$2\frac{1}{2}$	Cured
	31 F	Schizophrenia (paranoid)	5	3	$2\frac{1}{2}$*	Unchanged. Leuc tomy 9 months lat
	35 M	Obsessional neurosis	5	O.P.	$2\frac{1}{2}$	Much improved
	44 M	Anxiety neurosis	6	O.P.	$2\frac{1}{4}$	Improved
5	29 F	Anxiety neurosis	3	3	$2\frac{1}{4}$	Cured
	42 M	Obsessional neurosis	9	O.P.	$1\frac{3}{4}$	Improved
	48 F	Depressive state	20	2	$1\frac{3}{4}$*	Unchanged. Leu tomy 9 months la

* Follow-up includes period after further operation.

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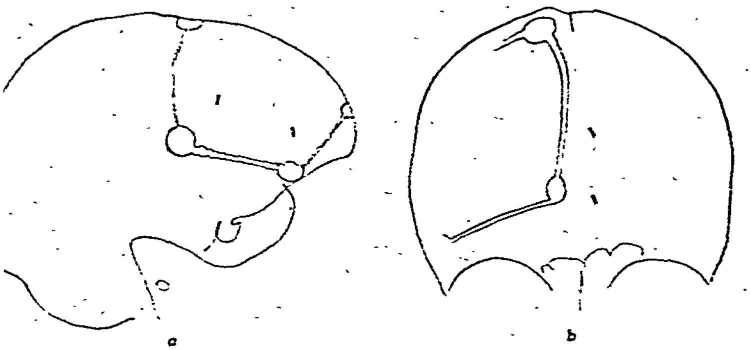
[3] Further psychiatric details of these and other cases will be given in a later report.

[4] In 2 of these patients the operation produced the des effect, but in the other 3 it failed to give much relief.



.4a and b—Postoperative X-ray tracing showing bone flap and silver clips which indicate e extent of the excision of cingular gyrus. The clips were placed at the anterior and sterior ends of the excision of the left gyrus (case 4.)

also four years after leucotomy. In the schizo- enics the operation did not lead to any lasting overy.

EIGHT CASES WITH WELL-PRESERVED PERSONALITY

(Table II)

From this preliminary experience we were satisfied it the operation was reasonably safe and free from rmful side-effects. Henceforth we selected only those tients with basically well-preserved personalities who d only superficial psychotic symptoms or prolonged, sabling, and intractable psychoneuroses with obsessive d anxiety features.

Case 4 (referred by Dr. William Ogden).—A married oman, aged 38, with two children, had been troubled with vere obsessive ruminations about the wickedness of sex for me twenty-three years. She was a woman of superior ility and poor education who had had a strict religious bringing and had been frightened and disgusted by planations about sex from her mother. She had married 27 and thereafter was a very active housewife, excessively rticular about cleanliness; but sometimes her obsessive oughts had been so severe that she could carry on none of r normal activities and remained shut in her room. On veral occasions she sought psychiatric advice. At the e of 35 the thoughts became so oppressive that she "col- psed," shouting and screaming, and later became stuporose. he was admitted to a mental hospital shortly afterwards a tense, agitated state, with a stream of semicoherent talk out sex and religion. She improved after E.C.T., but er obsessions returned soon after she went home, so that he was quite unable to look after children or home. At times he was severely depressed, and in the next three years she ad two more periods in hospital, where E.C.T. gave temporary nprovement, though it also affected her memory.

In 1949 she was again admitted in a state of tense agitation. ler ruminative obsessions became unbearable, and her istress was made worse by her insight into her condition and he failures of previous treatment. During the thirty-two onths before operation she spent half her life in hospital and ad 62 E.C.T.S; for months she had not slept without 'Sodium mytal.'

Cingulectomy was done in May, 1949. On the sixth day fter operation this patient had two short fits, and the electro- ncephalogram showed many subclinical attacks. During the irst month her ruminations were still present, but there was a narked reduction in tension and distress. In the next three nonths the thoughts gradually faded out. She had no more its. She took a full and active part in home life. Her usband and friends regarded her as cured, but her obsessions ecurred briefly on two occasions. However, two years after peration they had cleared entirely. Psychometric and Rorschach tests showed improved performance and dis- appearance of signs of introspective effort. She felt, and was, able to cope fully with life as she had never done before. No personality change was apparent to friends, but her husband thought she was occasionally irritable and less considerate for others than before operation. To detailed psychiatric examination she appeared cured.

Case 5 (referred by Dr. Ian Skottowe).—A married woman, aged 29, with three children, had been well and had survived severe air-raids on London without breakdown until three years before she was seen in March, 1949. Then, after an abortion, probably self-induced, she became anxious and depressed, with much guilt feeling. Symptoms became so severe that she was admitted as a voluntary patient to a mental hospital. She returned home improved after E.C.T., but rapidly relapsed and made a suicidal attempt which caused her readmission. She improved a little with continuous narcosis and insisted on going home. However, she still had much tension and anxiety and would get "panicky" feelings if she had to make decisions or do anything unusual. She could not face looking after her children, who were boarded out, though she wept bitterly at not being able to do so. She was depressed and at times mildly suicidal. She required large doses of sedative. She had good insight and was well preserved in intellect and personality.

Cingulectomy was performed in September, 1949. In the following month she was less tense, less overtly depressed, and no longer had any panicky feelings. "But," she said, "the real test will come when I get the children back." Although affect seemed slightly flattened and she took little part in hospital activities, she was improved, though not dramatically so.

She went home a month after operation and soon took charge of her children again. She managed them well. No panics recurred, and her feelings of dread and hopelessness had cleared entirely. She thought that she was a little more quick-tempered and had not so much drive as before her illness. This was confirmed by her husband, but the symptoms were slight and he regarded her as cured. Improvement in small ways continued for several months, and when seen in May, 1951, she was virtually symptom-free and leading a normal, happy, married life. When her husband went to hospital with appendicitis she was able to cope with the worry and extra physical effort involved. She did all her own housework and in addition she was doing outside domestic work two mornings a week.

These two women, both of them examples of severe tension and anxiety, the one with obsessive ruminations and the other with a mixed anxiety-depression, appear to be cured after cingulectomy. In both patients the retention of normal insight had heightened the distress of their state before operation. At that time each was taking large amounts of sedatives and had numerous maintenance courses of E.C.T. Since operation not only have the acute symptoms been relieved, but the preceding milder obsessions and depressions have also disappeared. The husbands say that their wives are better now than at any time in the past, and the personality of the patients, as judged by psychiatric and psychometric examinations and numerous interviews with relations and friends of the patients, seems to be little, if at all, disturbed.

The remaining 6 cases in this group have not given such marked success. Four (an anxiety depression, an acute anxiety state with compulsive behaviour, and 2 obsessionals) are substantially improved: 2 of them are at work and 1 of these is now approaching a good social recovery. Two (a depressive, and a schizophrenic with paranoid features) were unchanged after cingulectomy, and both have since had a standard leucotomy, the former with no appreciable change, the latter with a satisfactory short-term result.

Whereas after operation the chronic group usually showed an early temporary improvement followed by lasting relapse, in the group with preserved personality the improvement has appeared to be for the most part gradual and progressive. In these cases in the early months after operation psychotherapy was employed with considerable benefit.

Other Postoperative Changes

Sex Behaviour.—Attitude to sex after operation, which was investigated only in the well-preserved group, varied.

Often it was unchanged; sometimes its expression was less inhibited, seemingly because of the removal of secondary anxiety or obsessions; more rarely basic libido seemed slightly reduced for a time.

Somatic.—Apart from mental and behaviour changes, bodily changes also occurred in some of the psychotic cases. Thus, increase in weight was sometimes noted. The patients' weight was recorded for some weeks before and for six months after operation. Patients lost a few pounds postoperatively, but after this they steadily regained, and often exceeded, their former weight. Mean figures for the group showed less marked gains than those for a comparable group after leucotomy. In at least one patient (who was leucotomised after cingulectomy) there was a gain in weight of over a stone after the leucotomy, whereas only a small increase had followed cingulectomy. Nevertheless, in some cases substantial though temporary increases did occur after cingulectomy.

Pulse-rates were taken nightly, with the patient at rest, for three weeks before and six weeks after operation. No statistically significant change was observed in the aggregate. However, in case 1, whenever the patient was interviewed by a doctor preoperatively his resting pulse-rate was 120–130, and the apex-beat was forceful and heaving; after operation readings of 60–80, comparable with the preoperative nightly rates obtained by the nursing staff, were recorded during interviews.

Blood-pressure was recorded twice weekly before and for three months after operation, but unfortunately it was not always practicable to obtain an adequate series of preoperative readings for comparison. When one considers the normal variations in blood-pressure and its tendency to fall as the patient becomes familiar with the procedure, no significant variation emerges.

In general, the *levels* of these autonomic functions seemed little changed by cingulectomy; but whether any alteration occurs in the patients' ability under stress to maintain homœostasis about their base-line is uncertain. The difficulty is to devise suitable methods of measurement for use in the disturbed and uncoöperative patient.

Epilepsy.—Epilepsy has not been a serious complication of cingulectomy.

7 of the 29 patients had fits after operation, including 3 who had had none before. Of these, one was the patient who died and in whom the fits may have been caused by infection at the site of operation; another was a catatonic schizophrenic; and the third was a psychoneurotic (case 4). The fits occurred within the first week after operation in 4 of the 7 cases, on the ninth day in another. They were confined to the immediate postoperative period in all but 3 patients, each of whom had had fits before operation. The effect of operation on the course of the epilepsy in these 3 patients varied: in one there was no change; in another, an imbecile girl aged 20, epileptic since the age of 7, the incidence of fits became much less in the two years following operation, but was then as frequent as before; in the third patient, a schizophrenic whose illness progressed after cingulectomy, fits occurred at the rate of 3 to 4 a year in the two years after operation, whereas before operation he had only had one spontaneous fit.

Incontinence.—Persistent incontinence of urine, such as sometimes follows leucotomy, does not appear to be a complication of cingulectomy.

Of our 29 cases 12 showed some enuresis after operation; 5 of these were also incontinent of fæces. However, except when present before operation, these were always transient phenomena, usually occurring only in the first week after operation. Of the 12, 3 who were preoperatively incontinent still had this symptom after operation, but it was temporarily improved; the change ran pari passu with their clinical psychiatric state, and as this relapsed so incontinence increased again. In 1 patient with a severe agitated melancholia the incontinence of urine and fæces which had been present before operation was much worse for the first two months after operation, and then gradually returned to the p operative state in the next four months. Of the 8 others on 3 were incontinent three months after operation.

In the well-preserved group no incontinence persist after the first few postoperative weeks.

Sleep.—The operation does not appear to influen sleep directly. While their psychological improveme lasted, some of the psychotics slept without hypnoti In 3 psychoneurotics a more striking and permane change occurred. Before operation insomnia had be so severe that they had always contemplated the nigh with misery and dread. In 2 of these there was a su den return to normal sleep rhythm immediately aft operation, and this was maintained. In the 3rd, equal improvement occurred, but gradually, over t first postoperative year.

Sedatives.—All patients were receiving some sedati before operation, some in doses as large as 20 grains barbitone or 9 grains of sodium amylobarbitone a da During the first year after operation about one-third the patients showed a sustained reduction in the amou of drugs required. Of 9 disturbed and disorderly patient for instance, 3 have now done without their hyoscin and amylobarbitone for nearly a year. All the psych neurotics are taking significantly less sedative. Of the regarded as cured, who used to take large doses bot by day and night, one now takes none, and the othe prefers to have some phenobarbitone by her, though i fact she scarcely ever takes it.

POSTOPERATIVE PSYCHOTHERAPY

We must emphasise that in the psychoneurotic grou we consider that early after operation psychotherapy of great importance. The improvement after operatio is not dramatic: tension is less, but does not immediatel disappear as it may do after standard leucotomy. Th obsessions and anxieties are still present, and the patien whose insight is preserved does not face the futu resumption of ordinary life with any degree of confidenc Moreover, for one reason and another, he is in a recepti state for psychotherapy. The return to work is ofte attended also by social problems, and these are be gone into before the operation is done; afterwards the require continuous attention until the patient is onc more in his stride.

Discussion

In the 29 cases discussed here, although the whol of area 24, as shown in Brodmann's map of the huma cortex, was not removed, the major part of it wa destroyed bilaterally in most cases. No obvious neuro logical change occurred, nor was there any immediat dramatic change in behaviour, such as is seen in animal or in mental function. Our observations in the immediat postoperative period were not close and systematic, an autonomic and behaviour changes of a more subtl nature may have escaped us. However, there wer undoubtedly psychological and behaviour changes o some sort in nearly every case.

These changes are not always easy to describe. In few cases transient confusion, especially for time sequence, has been noted; and there was a tendenc sometimes for patients to speak and behave as if the did not know they had just had an operation, though i questioned directly they might pay lip-service to thi fact. There was also a lessening of tension and anxiety. In the psychotic group inaccessible patients becam accessible for a time, their behaviour became mor spontaneous, and aggressive outbursts were absent; bu these effects were transient, just as were the behaviou changes we had noted in monkeys (Glees et al. 1950 and in certain of the schizophrenics they had n perceptible effect on the progress of the disease.

In the psychoneurotic cases the changes were not at once dramatic. Obsessions and anxieties continued, but there was an immediate lessening in the amount of attention paid to them by the patient: they no longer obtruded continually in all conversation, nor were they associated with so much tension. This change tended to increase as time went on, and after some months obsessions and anxiety had disappeared or were greatly decreased, with the result that these patients became more accessible to psychotherapy, which itself helped the improvement.

A striking feature about the results of this operation is the absence of undesirable change in the personality of the patient often seen after standard leucotomy. Where personality has been changed for the worse, the effect has always been small; and the patient is not worse off, even when there has been but little relief from illness.[5]

Thus, the bilateral ablation of an area on the medial surface of the frontal cortex which, even allowing for some spread of damage from secondary vascular changes and manipulation of the brain at operation, must be regarded as relatively small, has produced definite though sometimes transient changes in the mental symptoms of almost all our patients. In some the consequent change in behaviour has been considerable, though there has never been the dramatic alteration seen in experimental animals.

Our experience suggests that the operation has little place in the treatment of advanced psychotics, but where anxiety and obsessions in a basically well-preserved personality are so intransigent and disabling as to require consideration of psychosurgery, cingulectomy clearly calls for further trial. It may be argued that obsessional states are those which respond most readily to any form of psychosurgery. Even so, the strikingly slight postoperative personality changes in this procedure compared with other operations suggest it as especially worth trial; for it is in just these cases that blunting of personality will be a noticeable disadvantage.

Part of the improvement noted may have been the result of factors incidental to the operation, such as change of environment and régime, and increased attention from nursing staff; but the long-continued alteration amounting to cure in some cases must be regarded as a result of the operation itself.

These results differ from those obtained in monkeys. This is to be expected, for though similarity of neuronal connections in the brains of man and animals must be reflected in function at the physiological level, such similarity may not appear directly in the more complex neuronal integration represented by purposive behaviour.

Stimulation of area 24 in monkeys produces autonomic changes of a type associated with expression of emotion and also at times a widespread cortical "suppressor" effect, both of spontaneous electrical activity and of motor response to cortical stimulation. Extirpation results in a temporary but profound and striking change in behaviour which can best be summed up as a loss of fear reaction to stimuli which previously elicited it, and a lack of normal persistence of emotional response to disturbing situations.

Anatomical studies further suggest that this area has mainly intracortical connections (Glees et al. 1950). Such cortico-cortical circuits suggest a possible mechanism for maintaining and reinforcing cortical activity. Changes in animal behaviour following its extirpation would support such an idea and would also be in line with Papez's view (1937) that it plays an important part in the neuronal substrate of emotion. Our clinical results are also in keeping with these views. Greatest benefit undoubtedly occurs in the obsessional and anxiety neuroses—cases where abnormal persistence of cortical activity, both affective and cognitive, may form the core of the illness. That this type of case rather than the schizophrenics would be most affected by cingulectomy has already been suggested by Ward (1948b) in the light of his work on animals.

This is speculation, and knowledge of the precise part played by the cingular cortex in the normal cerebral economy of man must await detailed observation of more cases, especially in the early postoperative period. Nevertheless, our material already provides some clinical evidence for differentiation of function within the frontal cortex—a point of considerable interest to the current discussion on whether the results in leucotomy depend simply on quantity of frontal lobe put out of action or on interruption of specific pathways.

Summary

1. The operation of cingulectomy—the bilateral extirpation of anterior cingular cortex—has been performed on 29 patients with mental disease. There was 1 death due to operation.

2. The results in the first 24 patients (16 advanced psychotics and 8 with mental illness in a basically well-preserved personality) are given after a follow-up period of eighteen months to three years.

3. Changes in the mental illness followed in the majority of the cases. In the psychotics, however, this was transient, and no worth-while improvement was maintained. In the others definite improvement occurred in 6 of the 8 cases. In 2 of these (a severe obsessional and an anxiety state) improvement was so great and sustained that the patients are at present regarded as cured.

4. A striking feature of our results has been the very slight amount of any unwanted personality change of the type seen sometimes after leucotomy.

5. It is suggested that this operation requires further trial in certain types of mental illness marked by obsessions, tension, and anxiety, in which the basic personality is well preserved.

In this work we have received much help from our psychiatric colleagues, Dr. R. W. Armstrong, Dr. R. G. McInnes, Dr. W. Ogden, Dr. I. Skottowe, and their staffs; and also from Dr. Eliot Slater. Psychological testing was carried out by Miss May Davidson, Mrs. M. Elvin, and Mr. J. Cole. An especial debt of gratitude is due to Dr. Paul Glees for his constant help and advice.

REFERENCES

Allport, G. W. (1949) Personality. London.
Beck, E., McLardy, T., Meyer, A. (1950) *J. ment. Sci.* 96, 157.
Freeman, W., Watts, J. W. (1944) *Ibid*, 90, 532.
Fulton, J. F. (1951) Frontal Lobotomy and Affective Behaviour. New York.
Glees, P., Cole, J., Whitty, C. W. M., Cairns, H. (1950) *J. Neurol. Neurosurg. Psychiat.* 13, 178.
Le Beau, J., Pecker, J. (1950) *Sém. Hôp. Paris*, 26, 1536.
Mettler, F. A. (1949) Editor: Selective Partial Ablation of the Frontal Cortex. New York.
Meyer, A., McLardy, T. (1949) *J. ment. Sci.* 95, 182.
Papez, J. W. (1937) *Arch. Neurol. Psychiat.* 38, 725.
Scoville, W. B. (1949) *J. Neurosurg.* 6, 65.
Smith, W. K. (1944) *Fed. Proc.* 3, 42.
— (1945) *J. Neurophysiol.* 8, 241.
Spiegel, E. A., Wycis, H. I. (1949) *Proc. R. Soc. Med. Suppl.* 42, 84.
Ward, A. A. (1948a) *J. Neurophysiol.* 11, 13.
— (1948b) *Res. Publ. Ass. Nerv. Ment. Dis.* 27, 438.

"... Today we hardly ask how large space is, but whether it is open or closed itself. We say that rubber stretches because its atoms are strung out in chains, and a diamond does not because the atoms are locked in a closed pattern. We believe that the enzymes in the body fit the chemicals which they rebuild as a key fits a lock, and when we are asked why bacteria absorb the sulpha drug on which they cannot grow we answer that the drug deceives them: its molecules have the same shape as the body chemical which the bacteria seek."—J. BRONOWSKI, *The Observer*, Feb. 24, 1952, p. 4.

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[5] And in such cases, as we have seen, standard leucotomy can be done later with satisfactory result.

DIETETIC AND OTHER METHODS IN THE TREATMENT OF PEPTIC ULCER

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IN the past twenty years many advances have been made in the surgical treatment of peptic ulcer, but the medical care of this disorder has undergone little change. Of the value of the conservative methods used there is at present little evidence, and I have therefore attempted to study some of them critically.

Up to the beginning of this century Leube's starvation régime was the customary treatment for gastric ulcer, and the suggestion that frequent small feeds might be beneficial was first made by Lenhartz in 1901 at the Congress of Internal Medicine at Wiesbaden. The barium or bismuth meal had not yet been introduced, and the diagnosis of peptic ulcer was based largely on the presence of blood in vomit and stool. It was thus essentially for the treatment of hæmatemesis that Lenhartz recommended his method, and in effect he introduced what Meulengracht (1935) reintroduced some thirty years later.

Lenhartz (1904) was chiefly concerned to prevent recurrences of the hæmorrhage, for he notes that only 4 of his 60 patients relapsed, and compares this with a 20% relapse-rate in patients treated by Leube's method. He did, however, mention that 35 of his 60 patients were free from pain, and that in 23 of the remaining 25 pain disappeared in three to fourteen days. Many who flocked to Lenhartz's clinic at Eppendorf in subsequent years wrote of the excellent results achieved, but all were interested chiefly in the prevention of the recurrence of hæmorrhage.

Haberman (1906) stated that all the 135 patients treated by him up to that time had had one or more hæmatemeses before treatment, and in only 8% had these recurred subsequently.

Langdon Brown (1908) considered the Lenhartz diet an improvement on starvation and rectal feeding for gastric ulcer with hæmatemesis, and Lambert (1908) came to a similar conclusion about gastric ulcer with occult hæmorrhage.

More than half the patients treated in those days were completely free from pain, and it seems likely that few had a definite ulcer of the type now treated with the Lenhartz régime.

When it became possible, after the introduction of the bismuth meal, to diagnose peptic ulcer in the absence of hæmorrhage, the Lenhartz diet not unnaturally came to be used in this type of case also. Subsequent modifications, such as those of Sippy and Hurst, were introduced later; and though no very serious effort seems to have been made to assess the therapeutic value of these methods, the "ulcer régime" typified by these diets has remained the routine treatment to this day.

Doubt was cast on the value of the ulcer régime by Ronald (1939), who compared cases of duodenal ulcer treated with frequent light meals and those receiving Sippy diet and antacids. Although there was a greater reduction of free acid in the latter group, the ulcers healed at about the same rate in both.

Nicol (1942) compared cases of peptic ulcer receiving a strict diet and alkalis with those receiving a full diet of four meals a day. (In the latter diet any rough articles were sieved.) In both groups the average duration of stay in hospital was four weeks. In 2 patients on full diet in which healing was observed by gastroscopy it was complete in six or seven weeks. Nicol concluded that results were as good, if not better, in those receiving a full diet. He had previously shown (Nicol 1939) that a full meal gave better control of acidity.

PRESENT STUDY

To get a clear idea of the effects of current methods of treatment a controlled study was undertaken. Alternate cases of peptic ulcer (duodenal, gastric, or were treated on the Lenhartz régime, the remaind receiving a normal convalescent diet. The modifie Lenhartz régime was used, consisting of diets 7-1 of the original Lenhartz scheme as recommended Mottram and Graham (1948) and now co employed in most hospitals. In this the original Lenhartz diet 7, consisting of milk and eggs only, is given during the first week and is augmented according to progress, generally when the patient has remained free from pain for at least four days on the previous stage. This plan was adopted in the "treated cases" in this study. Those on full diet had the ordinary hospital meals (including fried foods, cheese, and pork pies) without sieving or special preparation of vegetables and fruit. Some of the patients in this group who had previously received dietetic treatment were at first dubious of a régime so much at variance with their earlier instructions. When, however, it was explained to them that such food was required to inactivate their over-potent gastric juice, their anxiety was allayed, and the rapid relief of pain which followed in most instances quickly dispelled their doubts. In some cases the content of free acid and pepsin was studied for twenty-four hours during the treatment to compare the control of peptic activity under these two régimes. The value of rest in bed, of a milk drip, and of withholding tobacco was studied. Though it was desired also to study the effect of antacids on the rate of healing of the ulcer, I did not think it justifiable to omit antacids throughout the treatment of any patient, in view of the relief of pain which these afford. Accordingly, as an initial study, all the patients were given short periods of treatment on various antacids, and these were compared with a neutral placebo—barium sulphate.

EFFECTS OF ANTACIDS

As table I shows, each of the antacids studied gave greater relief from pain than did the placebo. The greatest relief was obtained from magnesium trisilicate, which abolished the pain in 53% of cases, against 13% with the placebo. The differences are statistically significant for magnesium trisilicate and magnesium carbonate but not for aluminium hydroxide. Table II shows the statistical data. As the order of giving the test substances was varied from case to case in regular sequence, there is no reason to suppose that the pain was more severe when the placebo was given. Moreover no indication was given to the patient of the relative action to be expected.

A study of the times required for complete relief of pain (where such an effect was obtained) confirms these findings. It proved shortest for magnesium trisilicate (18 minutes) and longest for the placebo (35 minutes). Aluminium hydroxide and magnesium carbonate gave intermediate times (23 and 27 minutes respectively). Sodium bicarbonate, as would be expected from its greater solubility, was most rapid in action (10 minutes).

TABLE I—VALUE OF ANTACIDS IN RELIEVING PAIN IN PEPTIC ULCER

Placebo or antacid	Dose	Effect on pain			Relief factor* (mean)	No. of patients
		None	Relief	Abolition		
Barium sulphate	ʒi	14 (45%)	13 (42%)	4 (13%)	1·0	31
Aluminium hydroxide	℥½	6 (50%)	3 (20%)	4 (30%)	1·3	13
Mag. carb. lev.	ʒi	4 (15%)	13 (50%)	9 (35%)	1·7	26
Mag. trisilicate	ʒ½	5 (13%)	13 (34%)	20 (53%)	2·0	38

* No relief = 0.
Relief = 1.
Greater relief, where two antacids give relief but the patient considers one more effective = 2.
Abolition = 3.
Aluminium hydroxide was not given in some of the earlier cases.

TABLE II—COMPARISON OF ANTACIDS AND PLACEBO

Antacid compared with placebo	Standard error of difference, (%)	Observed difference (%)
ag. trisilicate	10	40
ag. carb. lev.	11	22
luminium hydroxide ..	14	18

EFFECT OF DIET ON ACIDITY OF GASTRIC JUICE

In 20 patients the free acid in the gastric juice was stimated at hourly intervals for twenty-four hours, Ryle's tube being left in position throughout the test. 2 of these patients were on the Lenhartz régime and on full diet. Antacids, atropine, and olive oil were dministered in the same way to both groups (see below). he drug régime was thus identical in control and treated roups.

Free acid (table III) ranged from 0 to 110 in the control roup and from 0 to 90 in those on the Lenhartz régime. ean values were slightly lower in those having the enhartz diet. This applied to both day and night values. s however, the control group showed a higher maximum cidity during the initial fractional test-meal, no significance can be attached to this finding. It is interesting to note how little the acidity on gruel test is related to the values during treatment in individual cases, and therefore how unreliable an indicator the fractional test-meal is of the patient's normal state.

TABLE III—MEAN VALUES FOR FREE ACID ON LENHARTZ AND FULL DIETS

Case no.	Diet	Day mean	Night mean	24-hour mean	Maximum on initial fractional test
1	Ordinary	35	44	39	70
2	,,	49	55	52	..
3	,,	41	17	29	105
4	,,	42	60	51	25
5	,,	38	50	44	75
6	,,	29	18	23	70
7	,,	22	14	18	..
8	,,	50	30	40	..
9	,,	11	30	20	..
10	,,	18	25	22	40
11	,,	12	33	23	..
12	,,	18	16	17	75
13	,,	10	..	..	65
Mean	..	29	33	31	66
14	Lenhartz	34	18	26	..
15	,,	30	47	36	70
16	,,	16	..	..	60
17	,,	42	47	45	80
18	,,	1	3	2	10
19	,,	23	33	28	..
20	,,	27	29	28	..
21	,,	29	55	42	..
22	,,	21	9	25	90
Mean	,,	25	30	28	62

In 4 patients the pepsin levels in the gastric juice were studied during treatment. The mean values in treated and control cases were almost identical (table IV), but higher maximal values were found in those receiving a full diet. The pepsin values were highest at 9 A.M. —i.e., two hours after breakfast. They remained low throughout the day and rose again to about the same level soon after midnight. The amount of free acid showed synchronous changes, but the values at midnight were greater than those after breakfast.

NATURE OF THE THERAPEUTIC TRIAL

The effect of diet on pain and on healing of the ulcers has been studied in 140 patients, 70 of whom received the Lenhartz régime and 70 the ordinary hospital diet. The method of selection was by placing alternate patients on the Lenhartz régime and the remainder on ordinary diet. In the two groups drug treatment was the same, each patient receiving one drachm of magnesium trisilicate or of magnesium carbonate two-hourly throughout the day and, if awake, at night. In addition atropine in maximum-tolerated doses (usually gr. $^1/_{30}$) and olive oil $^1/_2$ oz. were each given thrice daily alternately by mouth. Those on full diet were allowed a glass of milk at 9 A.M. and at bedtime and also during the night if in pain. Those on ulcer diet received the usual two-hourly feeds throughout the day. 5 of the control and 6 of the treated patients remained ambulant throughout; the remainder were kept in bed till the ulcer was radiologically healed, except that they were allowed up for an hour each day after the first week of freedom from pain. During the latter part of the experiment alternate treated and alternate control patients received a milk drip throughout the night. This consisted of 2 pints of citrated milk containing 2 oz. of an aluminium-hydroxide suspension ('Aludrox').

TABLE IV—PEPSIN IN GASTRIC JUICE DURING 24-HOUR TEST IN 2 CASES EACH OF ULCER DIET AND FULL DIET

	Pepsin (mg. per 100 ml.)		
	Mean	Maximum	Minimum
Ulcer diet	100	130	0
	120	130	60
Full diet	130	330	0
	120	330	0

Patients were weighed weekly, and the stools were tested for occult blood once a week till the test became negative. No special dietary precautions were observed before the specimen of stool was taken. Despite this contravention of present custom, negative results were obtained in most of the patients whether on ulcer or ordinary diet, and in only 2 patients (1 in each group) did the test remain positive throughout the period of observation. Radiography was carried out at intervals of three weeks from the time that occult blood ceased to be present in the stools and was continued till evidence of an ulcer could no longer be detected. Gastroscopy was not undertaken, for it was felt that the discomfort and risk involved were not justified. Admittedly, "radiological healing" may antedate actual healing by some weeks, but though radiography does not give the actual date of complete healing, it will nevertheless give relative times of healing between groups of cases without bias towards one or other. The radiological studies were made by the radiologists in ignorance of the type of treatment the patient was receiving.

Table V shows the type of case studied in this experiment, as regards sex, age, duration, and site of disease. There was the usual predominance of males, the ratio being 6 to 1. In the control group 81% were males, in the treated group 89%. This difference is not significant, and there is no evidence that this slight predominance of males in the treated group affected the outcome: a study

TABLE V—INITIAL STATE IN CONTROL AND TREATED GROUPS

—	Control	Treated	Standard error
	70	70	
Sex:			
Males	81%	89%	6%
Females	19%	11%	
Age:			
Mean	43	45	
Maximum	86	78	
Minimum	20	18	
Site:			
Duodenal	46 (*66%*)	38 (*55%*)	4%
Gastric	20 (*29%*)	18 (*26%*)	
Gastric and duodenal ..	3 (*4%*)	10 (*14%*)	
Anastomotic and jejunal ..	1 (*1%*)	3 (*4%*)	
Jejunal and duodenal ..	0	1 (*1%*)	
Previous history:			
Mean	8·4 yr.	6·4 yr.	
Maximum	54 yr.	26 yr.	
Minimum	2 weeks	2 weeks	

of the final results showed that in the control group the average time of healing was sixty-eight days in males and seventy-one days in females. The age of patients varied between 18 and 86, the average age being 43 in the control group and 45 in those receiving the Lenhartz diet. A study of the site of disease showed that there was the usual predominance of duodenal over other sites, but that more of the treated group had a double lesion (gastric and duodenal), and that more of the controls had a solitary duodenal ulcer. There was also a greater proportion of anastomotic ulcers in the treated group (see below). The length of history showed wide variation, being less than a month in some cases, and as long as fifty-four years in one case. The average duration of symptoms was seven years, being two years longer in the control than the treated group. As, however, duration of history has been found to be unrelated to time of healing, this does not invalidate the subsequent findings.

An attempt was made to assess severity on clinical and radiological grounds before starting treatment, but it was found that the time of healing was in no way related to such an assessment, and in particular that the apparent initial size of the ulcer was not related to the time of healing. This assessment is therefore not included in the table.

RESULTS OF DIETETIC TREATMENT

Table VI shows that radiological healing was obtained in the same proportion in treated and control groups (93%), and the numbers improved, unchanged, and worse were similar. One patient died; he was aged 84. The time required for radiological healing averaged fifty-eight days in the control group and sixty-four days in the treated group. The ulcer thus took six days longer to heal in those treated with the Lenhartz diet. This difference is not statistically significant, but was present throughout the series; hence it is possible that, had sufficient cases been studied, a significant difference might eventually have emerged. Both minimum and maximum times of healing were also shorter in the control series. As, however, there was a larger proportion of multiple ulcers in the treated group, it must be considered whether a slower healing time in these could have been responsible for the difference observed. In fact, the multiple ulcers healed more slowly than the single ulcers in the treated group (av. eighty days) and more rapidly in the control group (av. forty days). The average time of healing for all multiple ulcers whether treated or control was seventy days, and for single ulcers sixty days. The inclusion of 10 multiple ulcers in a group of 70 cases as in the treated group would thus raise the average time of healing by only one day and could not explain the difference noted.

TABLE VI—EFFECT OF DIET ON COURSE OF DISEASE

—	Controls	Treated
Radiological healing:	65 (*93%*)	65 (*93%*)
Improved	3	2
No change	1	2
Worse	0	1
Died	1	0
Time required for radiological healing:		
Mean	58 days	64 days
Minimum	9 ,,	20 ,,
Maximum	153 ,,	189 ,,
Standard deviation	27 ,,	31 ,,
Standard error	3 ,,	4 ,,
Pain:		
No change	2	2
Improved	2	2
Abolished	66	66
Time required for abolition of pain:		
Mean	25 days	26 days
Minimum	0 ,,	0 ,,
Maximum	98 ,,	83 ,,
Epigastric tenderness:		
No change	1	1
Improved	1	1
Abolished	54	53
None present	7	9
Not noted	7	6
Time required for disappearance of tenderness:		
Mean	30 days	37 days
Minimum	3 ,,	5 ,,
Maximum	130 ,,	106 ,,
Occult blood:		
Not present	53	54
Ceased to be present	5	6
Unchanged	1	1
Not noted	11	9
Ceased in (mean)	24 days	23 days
Weight:		
Gained	22	25
No change	2	4
Lost	4	4
Not noted	42	37
Average gain/loss	+7 lb.	+5 lb.
Readmitted with recurrence:	10	7

Pain disappeared during treatment in 94% of cases in each group; it was improved in 3% and unchanged in 3%. The time required for disappearance of the pain was almost identical, twenty-five days in the control group and twenty-six days in the treated group. In both groups there were patients whose pain cleared up on the first day of treatment. In others there were many recurrences of pain before it finally subsided. In such instances the duration of pain was measured from the beginning of treatment till it finally subsided. The longest time taken for the pain to clear was ninety-eight days in a control, eighty-three days in a treated case.

TABLE VII—EFFECT OF MILK DRIP ON HEALING OF ULCERS AND DURATION OF PAIN

—	Milk drip	No milk drip
Total	12	13
Healed	10	11
Improved	1	1
No change	1	1
Time of healing (mean)	55 days	57 days
Pain: Ceased in	10	11
Improved	1	1
Unchanged	1	1
Duration of pain	22 days	27 days

Epigastric tenderness was noted in 80% of the control and 79% of the treated cases. It disappeared in all but 2 in either group, the mean time taken being thirty days in the control group and thirty-seven days in the treated group. In some instances it had gone by the third day; in one instance (a patient on ordinary diet) it required one hundred and thirty days to clear.

Occult blood was found in the stool in only 6 cases in the control and 7 cases in the treated group, clearing up in all but 1 in each group. The average times for this were twenty-four and twenty-three days respectively. Of those weighed before and after treatment, rather more of the treated patients gained, but the average increase was greater in the control group.

It was not found possible to follow up all these patients after discharge, because many were treated during the disrupting times of war. Actually 17 (12%) came to my notice in relapse, either in the follow-up clinic or through readmission to hospital. From other published statistics it is obvious that this is an underestimate. Rather more of the relapses were in the control group.

MILK DRIP

During the latter part of this investigation the effect of a milk drip was studied. It was found that the presence of a Ryle's tube in the œsophagus and pharynx was not readily tolerated for long periods. Inserted at night, however, and retained till the following morning (roughly eight hours) it caused after the first night or two no noticeable discomfort, and administration of phenobarbitone during the first few nights led to the treatment being acceptable to all patients. As it is at night that the highest values for free acid are found, and as control during the daytime is generally adequate, it seemed rational to give the milk drip at nights only. Two pints of milk were used. The milk was citrated and contained 2 oz. of aludrox. Altogether 12 patients received this treatment and are compared with 13 patients not so

ABLE VIII—EFFECT OF REST IN BED ON HEALING OF ULCERS AND DURATION OF PAIN AND TENDERNESS

—	Ambulant	Rest in bed
Total	11	129
Healed	10	120
Improved	0	5
No change	0	3
Worse	1	0
Died	0	1
Time of healing:		
Mean	86 days	64 days
Standard deviation	35	29
Standard error	11	4
Average duration of pain	37 days	25 days
Average duration of tenderness	28 ,,	32 ,,

treated. In each of these groups half the patients received a Lenhartz diet during the daytime, the remainder a full diet. Table VII shows the results of this method. There seems to have been a rather more rapid subsidence of the pain in those receiving the milk drip, but no striking acceleration of the rate of healing of the ulcers. The method, however, warrants further study in a larger series of cases.

REST IN BED

The effect of rest in bed was also studied in a few patients and the results are shown in table VIII. Of the ambulant patients 1 was worse after one hundred and eighty-nine days, the remainder reaching the stage of radiological healing. The time required for healing was very much greater in the ambulant patients (averaging one hundred and three days in the ambulant, sixty-four days in the recumbent patients). The pain was of shorter duration in the recumbent patients, but epigastric tenderness lasted longer. The number of ambulant patients is too small for statistical significance to be assessed. In a few instances tobacco was forbidden during treatment. This had no obvious effect on the rate of healing.

DISCUSSION

It would have been logical to continue this study till the difference between "treated" and "control" groups had either become statistically significant or had ceased to exist. Unfortunately, external circumstances made this impossible. I feel, however, that the absence of a beneficial effect from ulcer diet should be put down clearly and the suggestion of a harmful effect noted. In effect, the latter has been present throughout the study and I regard it as genuine. From a study of the acid and pepsin values it is clear that this effect is not due to more adequate neutralisation of acid or destruction of pepsin, and it must therefore be presumed that healing of the ulcer is assisted by some factor which is present in more adequate amounts in the less restricted diet taken by the control group. One advantage of a full diet is that it prevents the initial loss of weight and the distressing hunger of which the younger patients especially complain in the first weeks of the Lenhartz régime.

From these observations I suggest that patients with peptic ulcer should have three full meals each day, and that the quality and quantity of these should be in no way restricted. They should be such as to supply a well-balanced diet with ample roughage and adequate vitamins. In addition the patient should have 10 oz. of milk twice daily taken between meals and before going to sleep, the last in conjunction with a light supper. The milk may be taken as such or in the form of a warm *milk drink* such as cocoa or 'Ovaltine.' A glass of milk should also be kept at the bedside during the night, to be taken if the patient should wake up.

Antacids should be given two-hourly during the day and at similar intervals during the night if the patient is awake. One-drachm doses of magnesium trisilicate are recommended for this purpose. Atropine and olive oil may also be given, but there is at present no evidence that they hasten recovery. The patient should be kept at rest in bed till the pain has completely subsided, and then allowed up for an hour each day till radiological healing is complete. He should then be allowed up for increasing periods.

On discharge the following instructions should be given:

> Meals are to be taken at regular intervals. Not more than four hours should be allowed to elapse between meals, and preferably something should be taken every three hours. If a solid meal is not available, a glass of milk or a piece of milk chocolate may be substituted, but smoking should not be used to allay hunger. Rest should be taken for a short time after a meal, and when possible an hour should always be allowed for meal-times. For the first year after healing of the ulcer, antacid powders (such as magnesium trisilicate, a level teaspoonful) should be taken three times a day between meals, the last dose being taken at night before retiring. Should pain recur after the first year, regular doses of powder should be resumed, and a doctor should be consulted. During any illness which causes loss of appetite powder should be taken regularly.

SUMMARY

A series of 140 patients with duodenal, gastric, or anastomotic ulcers were studied to determine the value of medical methods of treatment.

Antacids produced a greater and more rapid relief of pain than did a placebo. Given in the usual therapeutic doses the order of effectiveness was: magnesium trisilicate, magnesium carbonate, aluminium hydroxide. The effect of antacids on the rate of healing of the ulcer was not studied.

Alternate patients were given an ulcer diet of the Lenhartz type. The remainder, known as the controls, ate the normal hospital meals.

Although the acid and pepsin content of the gastric contents was better controlled in those receiving the Lenhartz régime, the ulcer took, on the average, six days longer to heal (sixty-four and fifty-eight days respectively). The duration of pain and epigastric tenderness and the disappearance of occult blood from the stools was similar in treated and control groups, but the average gain in weight was greater in the controls (7 lb. against 5 lb. in the treated).

12 patients had milk administered through an œsophageal tube by continuous drip at night, and these were compared with 13 patients not so treated. The pain subsided more rapidly in the treated patients (twenty-two days against twenty-seven in the controls), but the time of healing was only two days shorter (fifty-five against fifty-seven in the controls).

11 patients were allowed up during treatment. These took twenty-two days longer to heal than those treated by complete rest in bed (sixty-four and eighty-six days respectively), and the pain took twelve days longer to subside (twenty-five and thirty-seven days).

It is concluded that the dietetic treatment of peptic ulcer as at present practised does not hasten healing and may delay it. *A less restricted régime is described and recommended.*

I wish to thank those radiologists who have kindly assisted me in this study, and in particular Dr. Martin Gray, at Haymeads Emergency Hospital. I also owe a debt of gratitude to those residents who have worked under me during the time of this study, and have borne without complaint the administrative difficulties which such a trial entails.

REFERENCES

Brown, W. L. (1908) *Clin. J.* 33, 109.
Haberman, J. V. (1906) *Lancet*, ii, 25.
Lambert, S. W. (1908) *Amer. J. med. Sci.* 135, 18.
Lenhartz, H. A. D. (1904) *Dtsch. med. Wschr.* 30, 412.
Meulengracht, E. (1935) *Lancet*, ii, 1220.
Mottram, V. H., Graham, G. (1948) Food and Principles of Dietetics. London.
Nicol, B. M. (1939) *Lancet*, ii, 881.
— (1942) *Ibid*, i, 466.
Ronald, J. (1939) *Brit. med. J.* ii, 1033.

A COMPARISON OF RADIOACTIVE AND METABOLIC METHODS OF INVESTIGATING THYROID FUNCTION

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The use of radio-iodine provides an entirely new approach to the study of thyroid activity. It was obvious from the outset that this test was not likely to run *completely parallel to older methods of investigation,* such as the basal metabolic rate (B.M.R.), and we have been concerned to find out the degree of correlation between the two tests, and to define any conditions likely to upset this correlation. The existence of such a correlation could not be assumed with safety from existing data, for two reasons: (1) the usual radioactive techniques measure uptake of iodine only and not output *of hormone**; and (2) the sensitivity of the tissues to* the hormone is unknown. Further, it seemed certain, from experiments made by Vander Laan and Vander Laan (1947) and others on animals, that various drugs would affect the two tests differently.

Werner et al. (1950) found little correlation in normal people between basal metabolism and neck uptake of I^{131} at 24 hours. Reiss et al. (1951a and b) reported *some degree of correlation but suggested that in certain* mental states the tissues may not respond to hormones secreted by the thyroid gland (Haigh et al. 1951, Reiss et al. 1951a). They used a method depending on measuring the urinary excretion, and thyroid uptake, of I^{131}. In addition, a general correlation over a wide range of thyroid activities between basal metabolism and the radioactive urinary-excretion test of Arnott et al. (1949) *has been demonstrated by Hobson (1951).* Some of the discrepancies between these reports may depend on different choice of clinical material, and some on technical details. It does not follow that results at one centre will necessarily be in agreement with those at another, if only because few places at present use the same technique for the radioactive studies.

METHODS

Our results, which have been briefly reported elsewhere (Foote, Mackenzie, and Maclagan 1951), were obtained by the following methods.

Basal metabolism was assessed in the postabsorptive state, after at least half an hour at rest, and in patients who had already had a trial run on the machine; we *used the standard Benedict-Roth oxygen-consumption* method, together with the Boothby and Sandiford (1929) age and sex tables. We have taken great care to obtain reliable estimates, and have required agreement between *duplicate determinations on the second day of test to* within 5%. The radio-iodine uptake was estimated by means of the thigh-neck clearance technique (Foote and Maclagan 1951). For three days before this test the patients were restricted to a diet poor in iodine and goitrogen, as previously described. As an addit precaution we obtained a urine specimen at the time *the investigation and tested it for iodides by the f* method, which is some ten times more sensitive th that previously given:

> In a test-tube place 1 ml. of urine, 1 ml. of $M/20$ sulphate in $10N\,H_2SO_4$, 1 ml. $M/20$ arsenious acid in $N/$ H_2SO_4, *and start a timer. Compare the colour with a con* tube containing 1 ml. of water in place of the arsenious ac Definite fading within 3 minutes indicates a concentration iodide *exceeding 100 µg. of KI per 100 ml. After* rece iodide therapy decolorisation is complete in a few seconds.

The only other difference in technique from th already published concerned the testing of hypothyro patients. The measurement of very low uptakes is mo *liable to error than that of normal or high uptakes,* a a somewhat longer period of observation was fou desirable in a few of these cases. When any doubt w felt as to the presence of a significant rise in the ne count, readings were continued for a sufficient peri (maximum 2½ hr.) to define the existence or otherwi of a definite slope. Cases showing no evidence of ne uptake have been reported as "clearance less than 0·1 *and have been calculated as 0·1 for statistical purpose*

The clinical material consists of a few normal peop and 162 patients (71 cases of definite thyrotoxicosi 18 of hypothyroidism, 4 of Simmonds's disease, a 69 euthyroid or doubtful). The diagnoses were bas *on clinical findings as defined previously* (Foote a Maclagan 1951) and were made without reference to t results of the tests.

RESULTS

Fig. 1 summarises the data on untreated patients i the form of a scatter diagram of 143 observations (140 cases ranging from thyrotoxicosis to myxœdem (thyrotoxicosis 52; doubtful or euthyroid 67; norm *persons 9; hypothyroidism 8; and Simmonds's disea* 4). In the cases of the three duplicated estimatio (two in thyrotoxicosis, one in Simmonds's diseas intervals of several months separated them. The norm ranges are shown as a rectangle, the limits bei 80–120% for the B.M.R., while for the thigh-nec clearance a range of 1–10 has been accepted as norma The clearances being plotted logarithmically, the regre*sion line becomes almost linear.* Assuming a straight-li

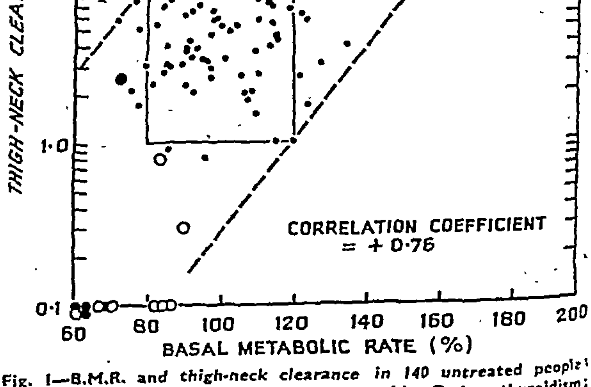

Fig. 1—B.M.R. and thigh-neck clearance in 140 untreated peopl: X, thyrotoxicosis; ●, doubtful or euthyroid; O, hypothyroidism; ●, Simmonds's disease.

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* An exception to this is the mea [illegible] plasma radioactivity, 48 hours afte [illegible] proposed by Goodwin et al. (1951) [illegible] present paper was in the press.

lationship, the correlation coefficient has been calculated and comes to +0·76 ± 0·035, thus demonstrating highly significant degree of correlation between these ests of thyroid function. In view of the approximation nvolved in calculating zero clearances as 0·1 this correlaion coefficient was also calculated after exclusion of hese 10 cases. This gave the almost equally significant igure of +0·70 ± 0·044. Though there is a fairly wide catter about the regression line, it is evident that the wo tests broadly confirm each other. Diagonal lines ave been drawn which include all the untreated cases, or comparison with the treated cases shown in fig. 2.

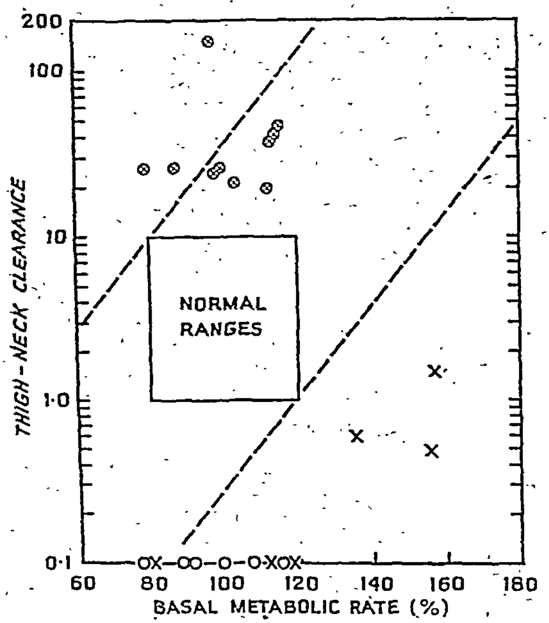

Fig. 2—B.M.R. and thigh-neck clearance in 22 treated patients: ⊗, goitrogens (thiouracil drugs 9, resorcinol 1); X, iodine; O, thyroid.

A direct comparison of the degree of overlap between the normal and pathological ranges for the two tests can also be made from fig. 1 with the following results:

Diagnosis	*No. of cases*	*No. within normal range*	
		Thigh-neck clearance	*B.M.R.*
Thyrotoxicosis	52	0	12
Hypothyroidism and Simmonds's disease	12	1	5
Euthyroid or doubtful	67	56	53

It is evident from this that the thigh-neck clearance can claim a definite advantage over the B.M.R. in this respect.

It is evident that from one case to another there can be a considerable variation of the ratio of the clearance to the B.M.R., and an attempt has been made, in a group of 49 of the thyrotoxic patients, to correlate this ratio with various features of the cases studied (the cases omitted had insufficient or doubtful data recorded). In this way the following possible associations were studied: age, sex, length of history, size of goitre, and degree of exophthalmos. None of these were found to have any significant association with the clearance/B.M.R. ratio.

Some further information on the thigh-neck clearance is shown in table I, which includes data accumulated on this test since our last report (Foote and Maclagan 1951). Some normal and hypothyroid persons are here included who do not appear in fig. 1 because the B.M.R. was not estimated. This table confirms our previous opinions of the value of this test in the diagnosis of thyroid disorders. Overlap between the normal range on the one hand, and the values in hypothyroidism and hyperthyroidism on the other, is still absent in this larger series. The results in myxœdema are particularly satisfactory in that all the 11 typical cases showed complete absence of iodine uptake (thigh-neck clearance less than 0·1). Of 3 further cases with zero clearance 2 had lately undergone thyroid surgery or irradiation.

TABLE I—THIGH-NECK CLEARANCE IN UNTREATED PATIENTS AND IN NORMAL PEOPLE

Classification	No. of cases	Mean clearance	Range	Logarithmic mean ± standard error
Normal people	25	3·6	1–10	0·48 ± 0·045
Thyrotoxicosis	52	48	13–137	1·60 ± 0·039
Hypothyroidism	16	—	0·1–0·8 (14 less than 0·1)	$\bar{1}$·09 ± 0·008*

* Standard error open to doubt owing to lack of normal distribution.

Fig. 2 shows the nature of the relationship between the test in 22 patients undergoing therapy of various kinds as follows: goitrogenic drugs (9 thiouracil or its analogues, 1 resorcinol) 10, iodine 6, thyroid or thyroxine 6. The patients under treatment with thiouracil or thyroid preparations showed complete remission of symptoms at the time of the test. It will be seen that goitrogen therapy increases the clearance/B.M.R. ratio, that iodine therapy decreases it, and that thyroid therapy in myxœdema raises the B.M.R. without affecting the zero clearance. These effects had, of course, been expected from the evidence accumulated by previous workers, but we hope that the quantitative relations illustrated here indicate more precisely the degree of alteration to be met with in practice with these particular methods of investigation.

Table II summarises our data on the thigh-neck clearance in treated patients and includes, besides those shown in fig. 2, a further 6, rendered clinically euthyroid by thiouracil or methyl thiouracil, but in whom no concurrent estimate of B.M.R. was available. It is interesting to note that this effect of goitrogens may long outlast the withdrawal of the drug. Thus in the case with clearance 150 and B.M.R. 98 (fig. 2) the drug had been omitted for six weeks before test, and in the case with clearance 27 and B.M.R. 88 it had been omitted for over three years before test. The differing trends of the two tests in treated patients is further indicated in table III.

TABLE II—THIGH-NECK CLEARANCE DATA IN TREATED PATIENTS

Therapy	No. of cases	Mean clearance	Range
Goitrogens ..	16	39	20–150
Iodine	6	—	0·1–1·5
Thyroid	6	0·1	All less than 0·1

DISCUSSION

With the techniques described here there seems to be a high degree of correlation between B.M.R. and thigh-neck clearance in untreated patients over the range of thyroid activities from myxœdema to thyrotoxicosis. The results support the belief that this radio-iodine method is valuable in the assessment of thyroid function, and this support is important because of the uncertainty of factors such as tissue sensitivity to hormone and relation of iodine uptake to output of hormone. In spite of this general correlation there is considerable variation in the results of the two tests in individual

TABLE III—LACK OF CORRELATION BETWEEN B.M.R. AND THIGH-NECK CLEARANCE IN VARIOUS FORMS OF THERAPY

Therapy	B.M.R.	Clearance
Goitrogens ..	Normal or low	High
Thyroid	Normal or high	Low
Iodine	High or normal	Normal or low

cases. This variation does not seem to be related to the length of history, the size of the goitre, the degree of exophthalmos, or the age or sex of the patient.

Our evidence in myxœdema is in keeping with the results of Johnston et al. (1951), who suggest that in the lower ranges of secretion the thyroid gland is an "all or none" organ—i.e., it either secretes normal amounts of hormone or secretes none at all. Thus we have only 2 cases showing appreciable subnormal uptake, and in 1 of these (clearance less than 0·3 B.M.R. 90%) the period of observation was insufficient to establish the clearance value exactly. All other cases of suspected hypothyroidism investigated had either zero or normal values for the thigh-neck clearance, the latter representing cases in which some other diagnosis was finally accepted.

The correlation between the two tests is close enough to make the exceptions to it very obvious, and the principal ones we have encountered have related to the administration of iodine, thiouracil, or thyroid hormone. In the first two examples the discrepancy arises from an alteration of iodine uptake, due mainly to isotope dilution in the case of iodine therapy and to specific interference with thyroid metabolism in the case of thiouracil. The relationship between thigh-neck clearance and goitrogen therapy is somewhat obscure and needs further study. In acute animal and human experiments with thiouracil the uptake of I^{131} is depressed, but with prolonged administration an increased uptake is noted parallel with the goitrogenic effect (Vander Laan and Vander Laan 1947, Stanley and Astwood 1947). This increased uptake persists after withdrawal of the drug, perhaps because of iodine deficiency. Our data suggest that this goitrogen-withdrawal effect may persist for as long as three years in man. In the case of thyroid therapy, on the other hand, the zero uptake of a true myxœdema is unaffected, and the normal uptake of a previously euthyroid person may be depressed.

In all these forms of treatment, therefore, the radioactive method may give anomalous results. Such results can, however, be of clinical value at times—e.g., in the case of secret thyroid administration, where the combination of a high B.M.R. and a low iodine uptake is very characteristic. It is obviously desirable to make a routine inquiry about treatment before making the radioactive test. As a further precaution we recommend the urine-iodide test described above.

It is probably too early to express any general opinion about the relative merits of the two procedures—the radio-iodine test and estimation of the B.M.R.—as diagnostic aids in thyroid disorders. The information which they give is complementary, but it can be said that in untreated cases the radio-iodine test which we have used appears to possess an advantage, since it exhibits less overlap between the normal and pathological ranges than can be claimed for the B.M.R. In treated cases, however, the older estimation is likely to retain its sphere of usefulness because its indications are not masked by the treatment, so that it can still be used, for example, as a guide to dosage in patients receiving thyroid or antithyroid drugs.

SUMMARY

The correlation between the B.M.R. and a radio-iodine test of thyroid function (thigh-neck clearance) has been examined in 9 normal people and 162 patients with various diseases of the thyroid gland.

In untreated people the two tests were strongly correlated (correlation coefficient = + 0·76).

There was a striking lack of correlation in patients receiving iodine, thyroid, or thiouracil-type drugs. The radioactive test gives anomalous results in patients so treated.

Some further results are presented on the thigh-neck clearance test in thyroid disease and they confirm our earlier opinion of its diagnostic usefulness. In the lower ranges of thyroid function the results suggest an all-or-none response by the gland.

We are indebted to the medical and surgical staff of the Westminster Hospital and to Dr. Raymond Greene for referring cases for investigation; to the physics department fo technical help; to Dr. P. W. Darby for some of the estimation of B.M.R.; and to Dr. T. Russell Fraser for helpful discussion on goitrogen therapy and urinary iodine tests. The work has been aided by a grant from the Governor's Discretionar Fund of Westminster Hospital.

REFERENCES

Arnott, D. G., Emery, E. W., Fraser, R., Hobson, Q. J. G. (1949) *Lancet*, ii, 460.
Boothby, W. M., Sandiford, I. (1929) *Int. physiol. Congr.* p. 32.
Foote, J. B., Maclagan, N. F. (1951) *Lancet*, i, 868.
— Mackenzie, D. H., Maclagan, N. F. (1951) *Proc. Soc Endocrinol* (in the press).
Goodwin, J., Macgregor, H., Miller, H., Wayne, E. (1951) *Quart. J Med.* 20, 353.
Haigh, C. P., Reiss, J. M., Reiss, M. (1951) *Proc. biochem. Soc.* xxv
Hobson, Q. J. G. (1951) T[illegible] of the Study o the Urinary Excretion [illegible] in the diagnosi of Thyroid Disease. [illegible]
Johnston, M. W., Squires, [illegible] F. (1951) *Ann intern. Med.* 35, 1008.
Reiss, M., Hemphill, R. E., Maggs, R., Smith, S., Haigh, C. P. Reiss, J. M. (1951a) *Brit. med. J.* i, 1181.
— Haigh, C. P., Hemphill, R. E., Maggs, R., Reiss, J. M. Smith, S. (1951b) *J. Endocrinol.* 8, 1.
Stanley, M. M., Astwood, E. B. (1947) *Endocrinology*, 41, 66.
Vander Laan, J. E., Vander Laan, W. P. (1947) *Ibid*, 40, 403.
Werner, S. C., Hamilton, H. B., Leifer, E., Goodwin, L. D. (1950 *J. clin. Endocrinol.* 10, 1054.

DICOUMAROL IN GENERAL PRACTICE

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THE purpose of this report is twofold. Firstly i suggests that in the treatment of thrombotic condition by anticoagulants the patient will gain little from keepin the prothrombin level below 20% of normal rather tha at 70% of normal. Secondly it suggests that in the long term treatment of these conditions dicoumarol ha certain advantages over 'Tromexan.'

DOSAGE

From theory and from experiment it has been concluded that a prothrombin level below 20% of normal i necessary both for the treatment and for the preventio of thrombosis (Barker et al. 1945, Wright et al. 194 Ball and Hughes 1949). But Burt et al. (1949) aimed a a prothrombin level of 20–30%; Peters et al. (1946 kept the level between 35 and 50%; and in the case I report here the levels were kept between 60 an 75% of normal. The results obtained by Burt et al. Peters et al., and myself seem to be much the same a the results in series where the level was kept below 20%

The reason for thinking this higher concentration o prothrombin adequate was that it had apparently bee effective in the following case, first reported by Scott an Lissimore (1944):

Case 1.—Between July, 1941, and June, 1943, this patien who suffered from lymphatic leukæmia, had many attack of mesenteric thrombosis of such severity that on sever occasions it was doubtful whether he could survive the shock In June, 1943, an account of the use of dicoumarol to comba thrombosis led to his treatment with this drug. Very graduall increasing doses were given with daily pathological contro When the prothrombin level was reduced to 70% of normal the patient ceased to have any further thromboses, and fo the remaining three years of his life he was kept on a dose o dicoumarol sufficient to keep his prothrombin level betwee 60 and 70% of normal. During this period he had n further suggestion of thrombosis, except once when o examination the prothrombin level was found to have risen t 85% of normal. On this occasion he had slight abdomina pain of the type he associated with a thrombosis, and suggestion of rigidity of the left rectus abdominis muscle.

At first the requisite dose of dicoumarol was 50 mg. on ternate days. but in the last year of his life this dose had to given every thirty-six hours to maintain the necessary ypoprothrombinæmia. Prothrombin tests in the last two ears were done monthly.

As a prothrombin level of about 70% of normal was ow enough to prevent thrombosis in one case. I thought would probably suffice to prevent thrombosis in others. ccordingly in giving dicoumarol in the home in 60 cases f sudden thrombosis, I have used a dosage designed to ower the prothrombin level to 60–75%. The conditions eated were :

Coronary thrombosis	38
Cerebral ,,	7
Venous ,,	11
Mesenteric ,,	4
Total	60

In sudden thrombosis treated at home dicoumarol 0 mg. is given twice a day for four days, after which the rst prothrombin test is done. In most cases the prohrombin level is then about 75% of normal, and the ose can be reduced to 50 mg. a day. If the level is still igh, the original dose is maintained. A test done after nother four days usually shows a prothrombin level etween 50 and 75% of normal. and often the dose is alved to 50 mg. on alternate days. Soon tests are made eekly, fortnightly, and finally monthly. The mainenance dose has varied from 100 mg. a day to 50 mg. wice a week. Only twice has a prothrombin level been ecorded less than 40% of normal. The urine is examined t the same time as the prothrombin tests are made—ishberg's test for kidney function being used as a imple and accurate test suitable for general practice. A atch is kept for clinical signs and symptoms of liver amage, because loss of kidney or liver function can apidly lower the prothrombin level.

During the first three days of treatment the dicoumarol ould not be effective, but in this series of 60 cases there ave been no deaths after the third day. 3 persons under reatment had thrombo-embolic complications : one aged 8 and one aged 69 had further small coronary infarcts, and ne aged 71 had a pulmonary embolism following his esenteric thrombosis. There was no case of hæmorrhage.

These cases have been briefly described to show that icoumarol can be used safely and usefully in general ractice, but most clinicians will probably prefer to use romexan, which is more rapidly absorbed and excreted nd therefore safer when a prothrombin level less than 0% of normal is aimed at. Dicoumarol has the dvantage of comparative cheapness.

The prothrombin estimations were all made in the same aboratory. In a few early cases the Witts-Fullerton technique as used, thromboplastin being produced from viper venom nd lecithin. Most of the tests, however, were done by uick's method, and this has twice been modified as advances n knowledge have occurred. Thus, though the actual prohrombin levels of my cases are not strictly comparable, hey are accurate enough to give a clear picture of the value f lowering the prothrombin to a safe level.

LONG-TERM USE OF DICOUMAROL

There is a strong argument for maintaining a lowered rothrombin level for a long time after an original sudden hrombosis. As the accompanying table shows, thrombo-mbolic complications are common after coronary hrombotic catastrophes.

Such complications are probably equally common fter cerebral and mesenteric thromboses.

If the primary cause of these thrombotic conditions is ot in the vessels themselves (Duguid 1948) but in a endency to thrombosis, a form of treatment which lessens he tendency of the blood to clot should prevent at least ome of them.

Blumgart et al. (1940) studied 355 cases of coronary hrombosis at necropsy and found that collateral circulaion was good in all long-standing obstructive coronary arterial lesions. An anticoagulant which will keep the patient with coronary thrombosis free from further thrombosis or embolism will therefore give him a chance to develop a good collateral circulation. This improvement in circulation has clinical support from the histories of those patients who have recovered from coronary infarction, and, one or two years later, begin to find an increase in their physical capacity.

THROMBO-EMBOLIC COMPLICATIONS AFTER SUDDEN CORONARY THROMBOSIS

Investigation	Investigators	No. of cases	Percentage of thrombo-embolic complications
Pathological	Hellerstein and Martin (1947) ..	160	45
,,	Foord (1948)	316	15·3*
Clinical	Nay and Barnes (1945) ..	100	37
,,	Barker et al. (1945)	678	43·8
,,	Wright et al. (1948)	368	36

* Pulmonary embolism only.

In the maintenance of hypoprothrombinæmia for a long time, dicoumarol is more useful than tromexan because it is more slowly excreted, and thus enables us to keep the prothrombin level steady on a dose of perhaps 50 mg. on alternate days or even twice a week.

Since 1944, I have treated 40 cases of thrombosis with dicoumarol as a preventive treatment against thrombo-embolic complications. They comprise 25 cases of coronary thrombosis, 11 of cerebral thrombosis, and 4 of mesenteric thrombosis. The shortest period of continuous administration of dicoumarol was six months and the longest three years. Some of the patients were treated continuously from October to March for up to four years. The reason for winter treatment was that from 1927 to 1948 there were 62 deaths in my practice from coronary and cerebral thrombosis, of which 52 took place between October and March, and only 10 between April and September. But later it was discovered that thrombo-embolic complications occurred fairly frequently during the summer months; so I now keep up the treatment the whole year round.

The aim has been to maintain the prothrombin level at between 60 and 75% of normal, and the results are interesting.

Results

Of these 40 patients given protracted treatment with dicoumarol, 15 have died. Of these, 1 died of coronary occlusion while under treatment. He was 82 years of age, and his prothrombin level was 72% of normal a fortnight before death. 9 died of thrombo-embolic complications during the part of the year when they were not under treatment with dicoumarol. Of the remaining 5 deaths, 2 followed acute bronchitis after "influenza," 1 was caused by carcinoma of bronchus, and 2 were due to renal failure. What is remarkable is that, while the prothrombin level was between 60 and 75% of normal, only one other thrombo-embolic complication has been noted—a small coronary infarct. That is to say that in a group of 40 patients, each of whom had had a thrombotic attack from one to four years previously, only two further thrombo-embolic complications (with 1 death) were recognised while the patients were under treatment with dicoumarol to this extent.

No hæmorrhage has occurred from using dicoumarol in this way. In 1944–46 4 cases of gastro-intestinal upset were recorded, and treatment was stopped after two or three days. No other ill effect from taking dicoumarol has been seen, and no gastro-enteritic upset since 1946.

A brief account of some of the cases in which the prothrombin level was kept between 60 and 75% of normal for a considerable period will help to give a picture of the apparent value of this treatment.

Case 2.—A woman, aged 72, had acute rheumatism in childhood. She has had angina of effort for ten years and is very limited in physical capacity. Between April, 1949, and December, 1950, she had five attacks of pain in the chest with pyrexia, followed by cough, sometimes with bloodstained sputum. She was put on dicoumarol and has had no further attack in fourteen months.

Case 3.—A man, aged 43, had a coronary occlusion while walking home through snow on a winter's night. He recovered and was kept on dicoumarol for six months. Next winter he again took dicoumarol for six months. In the third winter he did not report for treatment, and one cold winter's night in December he had a coronary occlusion after coitus and died in an hour. (The danger of coitus in cold weather after a coronary attack should be emphasised. I have seen three deaths caused in this way.)

Case 4.—A man, aged 90, had a cerebral thrombosis affecting his speech. He recovered, but two months later had a second attack affecting speech, left side of face, and left hand. Three months after this he had a third attack, affecting left arm and leg. He was put on dicoumarol, and eighteen months later he has had no further attack.

Case 5.—A man, aged 48, had a coronary occlusion. He took dicoumarol for three winters (each a six-month course) and though he developed a duodenal ulcer in the second year he did not have any obvious thrombo-embolic complications. The fourth winter he did not come for treatment, and, after an exciting business meeting in a warm room, he walked to a tramcar in a biting east wind. He was overcome by angina of effort and died in a few hours from coronary occlusion.

Case 6.—A man, aged 70, had hypertension; blood-pressure around 180/120 mm. Hg; and for five years had angina of effort. On walking in the cold he had a coronary occlusion; B.P. 106/70. He was put on dicoumarol until the summer. Next winter, before starting dicoumarol, he developed paralysis of the left side of face and left arm, from which he largely recovered. He has been on dicoumarol now for two and a half years without further incident.

No attempt at statistical analysis is made in so few as 40 cases. Chance can play so large a part. But the suggestion is strong that a prothrombin level of 60–75% of normal will prevent many a thrombo-embolic complication which would otherwise occur.

Note.—All the cases described as "coronary occlusion" or "thrombosis" were verified by electrocardiography, except in cases of sudden death, when there was no time to do so.

Almost all the prothrombin tests were done by one pathologist.

SUMMARY

A description is given of the successful treatment of a case of mesenteric thrombosis, in which the prothrombin level was kept between 60 and 75% of normal with dicoumarol.

Good results have followed similar treatment in coronary and other thrombotic episodes in 60 cases.

A prothrombinæmia of 60–75% of normal was maintained in 40 cases of thrombosis for periods of from six months to three years with no ill effects.

Clinically the occurrence of thrombo-embolic complications in the first year after coronary, cerebral, and mesenteric thrombosis is 30% or more. Of the above group of 40 cases, 2 (5%) had further thrombo-embolic complications while under treatment.

REFERENCES

Ball, K. P., Hughes, H. O. (1949) *Brit. med. J.* i, 560.
Barker, N. W., Cromer, H. E., Hurn, M., Waugh, J. M. (1945) *Surgery*, 17, 207.
Blumgart, H. L., Schlesinger, M. J., Davis, D. (1940) *Amer. Heart J.* 19, 1.
Burt, C. C., Wright, H. P., Kubik, M. (1949) *Brit. med. J.* ii, 1250.
Duguid, J. B. (1948) *J. Path. Bact.* 60, 57.
Foord, A. G. (1948) *J. Amer. med. Ass.* 138, 1009.
Hellerstein, H. K., Martin, J. W. (1947) *Amer. Heart J.* 33, 443.
Nay, R. M., Barnes, A. R. (1945) *Ibid*, 30, 65.
Peters, H. R., Guyther, J. R., Brambel, C. E. (1946) *J. Amer. med. Ass.* 130, 398.
Scott, R. A. M., Lissimore, N. (1944) *Lancet*, ii, 405.
Wright, I. S., Marple, C. D., Beck, D. F. (1948) *Amer. Heart J.* 36, 801.

FURTHER EXPERIMENTS ON THE PREVENTION OF MOTION SICKNESS

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A PREVIOUS experiment showed that 1 mg. of hyosci hydrobromide prevented seasickness in more men tha did 25 mg. of promethazine hydrochloride ('Phenergan' but the same experiment also produced some eviden that promethazine might be a better preventive f seasickness than other anti-histamine substances (Glas and Hervey 1951). The present investigation w designed to show whether larger doses of promethazi would equal or surpass the results with hyoscine, an whether combinations of promethazine and hyosci would be more effective than either drug alone. I addition, it seemed advisable to find out wheth hyoscine would prevent nausea and vomiting if it w taken a few minutes before the motion began, an finally, it seemed worth while to test drugs which increa the blood-flow to the brain; especially since McGowa et al. (1938) had claimed that glyceryl trinitrate cure vomiting during pregnancy.

MATERIAL AND METHODS

Subjects

The subjects of the experiments were 150 soldiers w had volunteered from different units all over Brita and were a representative sample according to t criteria previously given (Glaser and Hervey 195 They were divided at random into two groups, one 102 men and one of 48 men, and experiments were ma on these two groups.

Motion

In the past, whenever small boats were used f motion-sickness experiments at sea, the weather w an inconstant factor (Holling et al. 1944, Hill and Gue 1945, Glaser and Hervey 1951). In the present expe ment, therefore, a new method was tried by puttin inflatable rubber floats into a swimming-pool wit artificial waves. The motion was recorded with Dobbie McInnes accelerometer. Although the floa were anchored as close together as possible, the mov ments of different floats and of various parts of t same float were not always the same. The effects these discrepancies, however, were largely overco by the way in which the men were distributed ov the floats and moved about during the tests (see below The accelerations were between +0·17 and +0·43 and between −0·12 and −0·16 *g*. The period w 3·45 sec. The accelerations and periods were simil in this and the previous experiment, but the motio was more regular in the present one.

Drugs and Routine

The men's activities and the issuing and coding of t drugs were as carefully controlled as in the previo experiment. The substances again looked alike, and t containers were again marked with a code which tho conducting the experiment could not interpret until aft the results had been recorded. The floats were cover in, and the sleeve entrances at each end were eith shut or occupied by the N.C.O. or sailor keeping record The men were again sitting throughout each test, b they changed places every 15 min. to counteract slig differences in the motion in different parts of the float The floats always contained roughly equal numbe of men who had taken any particular substanc uestionnaires were completed after the tests as in the revious experiment, but this time some information ras also obtained about symptoms during the next ew hours after leaving the floats. Each group was ested on alternate weekdays, the men being exposed o motion every forty-eight hours, except for a seventy-wo-hour interval at the weekend. Each exposure asted an hour.

In the experiment on 102 men the following substances vere given:

(1) *l*-Hyoscine hydrobromide 1 mg.
(2) Promethazine hydrochloride 35 mg.
(3) Hyoscine hydrobromide 1 mg. with promethazine hydrochloride 25 mg.
(4) Hyoscine hydrobromide 0·65 mg. with promethazine hydrochloride 15 mg.
(5) Hyoscine hydrobromide 0·65 mg. with promethazine hydrochloride 15 mg. and mannitol hexanitrate 50 mg.
(6) Lactose (dummy substance).

It was intended to give each substance to 17 men on each experimental day and to give every man every substance in the course of the six days; but some men were absent on some days for reasons not connected with the experiment. It seemed safe to assume that all the drugs would be completely eliminated in forty-eight hours, but a scheme was nevertheless worked out according to which every substance was preceded by every other substance about the same number of times on each day except the first.

The experiment on 48 men was broken up into three separate tests:

(1) Before the first and sixth exposures to motion all the men were given a dummy substance to show whether fewer men were sick on the last than on the first day. The risk of adaptation was considered small (Glaser and Hervey 1951), but this test was included as a precaution.

(2) On the second experimental day half the men were given hyoscine hydrobromide 1 mg. one and a quarter hours before boarding the floats, and the others a dummy capsule; at the moment of boarding those who had had hyoscine were given the dummy capsule and those who had had the dummy were given hyoscine. On the third experimental day the order of issuing was reversed, so that those who had previously received the drug one and a quarter hours before boarding the floats now received it on boarding, and those who had previously received it on boarding now received it one and a quarter hours beforehand.

(3) Before the fourth and fifth exposures the men took nothing. If, however, they felt sick on the floats they were given a sublingual tablet by the observers. On both days glyceryl trinitrate 0·6 mg. was given to half the men and an indistinguishable dummy tablet to the others, but the drug was given to one half of the men during one test and to the other half during the next. Only the observers knew that there were two types of tablet, but not even they knew that one was a dummy.

Statistical Calculations

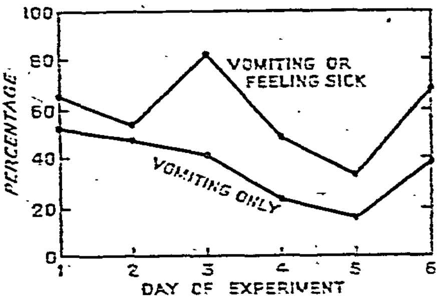
The χ^2 correlations, with a correction for continuity, were worked out according to Fisher (1944). When several substances are compared, statistical calculations are given for the least favourable comparisons only.

RESULTS

Adaptation and Side-effects

The accompanying figure shows that in the experiment on 102 men there was some decrease in the number of untreated men who vomited or felt sick. In the other experiment only 32 men were available on all six days; 15 of these (47%) vomited on the first day, and 6 (19%) on the last, while the number of those who vomited or felt sick was 18 (56%) on the first day and 10 (31%) on the last. Not all men became adapted alike. Moreover, some men who did not vomit after a dummy substance early in the series of exposures did so later after they had been given an active substance.

Headaches, drowsiness, and giddiness were about as frequent after the dummy substance as they were after any of the drugs or combinations of drugs, and they were noted about as often as in the previous experiment. Excitement was again equally rare after every treatment. The greatest number of complaints of dry mouth were recorded after the combination of hyoscine 1 mg. and promethazine 35 mg. (77%), but as many as 51% were recorded after the dummy substance. Complaints of "light-headedness," sleepiness, or mild gastro-intestinal disturbances a few hours after the tests were as frequent when the men had been given the dummy substance as they were after any of the active substances. The most frequent complaint of the men was about the smell of rubber in the floats, but these complaints became fewer towards the end of the experiment.



Percentage of men who vomited or felt sick after being given an inactive substance.

The observers' records suggest that men on the same float often vomited within a few minutes of each other, although men on different floats did not vomit at the same time. It therefore seems possible that some men were made sick by the sight of others being sick. This disagrees with observations made in the previous experiment.

Effect of Drugs

Table I shows that in the experiment on 102 men fewer men were sick or felt sick after any of the active substances than after the dummy. Similarly, fewer men vomited or felt sick after they had taken hyoscine alone or in combination than after promethazine 35 mg.

The differences between any of the active substances and the dummy are statistically significant ($\chi^2 > 12{\cdot}5$, $P < 0{\cdot}01$ for vomiting alone: $\chi^2 > 17{\cdot}4$, $P < 0{\cdot}01$ for vomiting or nausea). The differences between promethazine and any of the substances containing hyoscine are also statistically significant ($\chi^2 > 4{\cdot}16$, $P < 0{\cdot}05$ for vomiting alone; $\chi^2 > 4{\cdot}82$, $P < 0{\cdot}05$ for vomiting or nausea), with the one exception that the number who vomited after a combination of hyoscine, promethazine, and mannitol was not significantly smaller than the number who vomited after promethazine 35 mg. ($\chi^2 = 1{\cdot}90$, $P = 0{\cdot}1$ to $0{\cdot}2$). All the capsules containing hyoscine prevented vomiting and nausea in most of the men, and the differences between the

TABLE I—INCIDENCE OF VOMITING AND NAUSEA AFTER VARIOUS SUBSTANCES

Crossed-over experiment on 102 men

Substance given	No. of men treated	No. of men who vomited	% protected* from vomiting	Total no. affected by vomiting or nausea	% protected* from vomiting and nausea
Dummy	101	36 (36%)	..	58 (57%)	..
Hyoscine 1 mg.	98	3 (3%)	92	11 (11%)	81
Promethazine 35 mg. ..	99	13 (13%)	64	27 (27%)	53
Hyoscine 1 mg. with promethazine 25 mg. ..	97	2 (2%)	94	11 (11%)	81
Hyoscine 0.65 mg. with promethazine 15 mg.	99	4 (4%)	89	7 (7%)	88
Hyoscine 0·65 mg. with promethazine 15 mg. and mannitol hexanitrate 50 mg.	95	6 (6%)	83	13 (14%)	75

* (Holling et al. 1944).

TABLE II—EFFECTS OF TAKING 1 MG. OF HYOSCINE HYDROBROMIDE $1^1/_4$ HR., OR 5–10 MIN., BEFORE EXPOSURE TO MOTION

Time of taking hyoscine	No. of men who vomited	% protected from vomiting *	Total no. affected by vomiting or nausea	% protected from vomiting and nausea
$1^1/_4$ hr. before ..	3 (*6%*)	88	6 (*13%*)	78
5–10 min. before	7 (*15%*)	69	20 (*42%*)	30
Significance of *difference* ..	$\chi^2 = 1·01$ $P = 0·3$ to $0·5$	..	$\chi^2 = 8·21$ $P < 0·01$	..

* Calculated from the results when same group was given dummy substance on first day.

effects of these substances *are not statistically significant* ($\chi^2 < 1·57$, $P > 0·2$).

From two to three times more men approved than disapproved of any of the active substances or combinations, but twice as many men disapproved of the dummy as approved of it. Otherwise no differences were shown in the individual preferences.

Table II shows that fewer men were affected when hyoscine 1 mg. was given at the moment of boarding than when a dummy was being taken. (The men were exposed to full motion within five to ten minutes after they had swallowed the capsules. All 48 men were present on both days of this experiment.) If those suffering from nausea are included, the difference is statistically significant.

On the two days when glyceryl trinitrate was compared with a dummy tablet 16 men took each tablet; 8 of them vomited within half an hour of taking glyceryl *trinitrate, and 10 within half an hour of taking the dummy. More men approved of the dummy than* of the drug.

DISCUSSION

Although some men became adapted to the motion after the first few tests, some conclusions may be drawn.

All the substances containing hyoscine were more effective than promethazine 35 mg. Moreover, the proportion of those protected from motion-sickness by promethazine 35 mg. was about the same as that protected by 25 mg. in the previous experiment, and it seems probable that the best dose of promethazine as a preventive of seasickness is 25 mg. or less. It cannot be said from the present experiment whether combinations of hyoscine with promethazine or mannitol would be any better than hyoscine alone. Holling et al. (1944), however, found 0·6 mg. of hyoscine only moderately less effective than 1·2 mg. The possibility must, therefore, be admitted that hyoscine may have been largely responsible for the action of all the combinations which contained it in the present experiment. It seems unlikely, moreover, that mannitol hexanitrate should have any protective influence, since glyceryl trinitrate had none. It was useful, however, to find out that hyoscine taken a few minutes before the motion began was still moderately effective, though less so than when it was taken one and a quarter hours beforehand.

It has been suggested that promethazine might be more effective if more time was allowed for its absorption from the gastro-intestinal tract (Bethell 1951). This possibility *cannot be excluded, but the value of any remedy for* seasickness would be reduced if it had to be taken many hours before meeting rough motion.

The main reason for adaptation was probably the regularity of the motion. Some of the men may also *have become used to the smell of rubber and the sight* of others vomiting.

In conclusion it must be said that, except for pethidine (Burn 1951), all the likely remedies have been investigated during the last eight years in this country and in North America. No further improvements can be expected, except by accident or by a systematic study of basic principles.

SUMMARY

Experiments were made in a large swimming-b with artificial waves.

Promethazine hydrochloride (‘Phenergan’) 35 prevented vomiting and nausea in fewer men than hyoscine hydrobromide 1 mg. or hyoscine hydrobrom 0·6 mg. with promethazine 15 mg.

A comparison between the effects of hyoscine combinations of hyoscine with promethazine yiel no conclusive results.

Hyoscine 1 mg. given five to ten minutes before motion started was still effective, but less so than w it was given one and a quarter hours beforehand.

Glyceryl trinitrate did not prevent vomiting.

Our thanks are due to Prof. R. A. McCance, F.R.S., his help and advice; Surgeon Commander J. W. L. Cro R.N., for his help with the administrative arrangements *for useful suggestions; Mr. G. C. Maynard, for the accel* motor records; Mr. Norman Bailey, for advice over statist problems; and Mr. L. A. R. Luff, for help in running experiment. The tests were made in the Portobello Ba Edinburgh. We are also very grateful to the soldiers took part in the experiment and to the soldiers and sai who acted as observers.

REFERENCES

Bethell, M. F. (1951) *Lancet*, ii, 888.
Burn, J. H. (1951) Personal communication.
Fisher, R. A. (1944) Statistical Methods for Research Work Edinburgh and London.
Glaser, E. M., Hervey, G. R. (1951) *Lancet*, ii, 749.
Hill, I. G. W., Guest, A. I. (1945) *Brit. med. J.* ii, 6.
Holling, H. E., McArdle, B., Trotter, W. R. (1944) *Lancet*, i, 127.
McGowan, J. M., Baker, J. O., Torrie, A. M., Lees, J. (1938) *J. A med. Ass.* 110, 498.

Medical Societies

ROYAL SOCIETY OF MEDICINE

Medical Treatment of Hypertension

THE section of medicine of the Royal Society Medicine met on Feb. 26, with Sir ALUN ROWLAN president of the section, in the chair, to discuss medical treatment of hypertension.

Prof. M. L. ROSENHEIM remarked that five ye ago, when the section last discussed this subject, only available active medical treatment was administ tion of potassium thiocyanate. This has now b replaced by the hexamethonium drugs, veratrum p parations, and low-sodium diets; while surgery off sympathectomy, and also adrenalectomy, which still in an experimental stage. He emphasised th only a small proportion of hypertensive patients suitable for treatment with a low-sodium diet and hexamethonium compounds; mild cases should be treated in this way.

Essential ingredients in the medical treatment hypertension are reassurance, reorganisation of patient's mode of life, control of obesity, and sedati Low-sodium diets are of value only if strictly defined e.g., less than 200 mg. sodium or 500 mg. sodium chlori per day—and rigorously adhered to. The comm causes of their failure are inadequate sodium restricti and the patient's intolerance of such a régime. T Medical Research Council has confirmed Kempne main claims for his rice diet. About 70% of ca of essential and chronic renal hypertension showed good fall in blood-pressure, and a higher proporti *obtained symptomatic relief.* In some there was impro ment in eye changes, heart size, electrocardiograph appearances, œdema, and breathlessness. In re failure sodium restriction may be dangerous if t kidney's power to conserve sodium is impaired; a mercurial diuretics in conjunction with a low-sodiu diet can also cause serious sodium depletion.

Of the various drugs that block the transmission of sympathetic vasoconstrictor impulses at the ganglia, or antagonise the effect of adrenaline or sympathetic stimulation at the nerve-endings, hexamethonium has proved the most effective, although it is far from perfect. Others, such as tetraethylammonium salts, are too short in their action; some, like 'Priscol,' are more effective in the treatment of peripheral vascular disease and have little hypotensive action; while others, like 'Dibenamine,' are difficult to administer and too toxic for regular usage. Hexamethonium blocks the transmission of impulses in both sympathetic and parasympathetic ganglia; and while the first of these two actions is useful in hypertension, the latter produces certain side-effects, such as paralysis of accommodation, dryness of the mouth, constipation, distension, and occasionally difficulty with micturition. Fortunately, these side-effects are not usually severe, but occasionally they may lead to abandonment of the treatment. Pilocarpine is under trial to counter these side-effects; and neostigmine may be of value in dealing with abdominal distention.

The resulting fall in blood-pressure is largely due to the removal of abnormal vasocontrictor tone, but it is also partly postural. This postural hypotension may be troublesome, and most patients have to lie down for about an hour after an injection of the drug. Postural hypotension is an essential element in the effective action of hexamethonium, and is not to be regarded as a side-effect. A possible danger of producing widespread vasodilatation is that thrombosis will be favoured in anatomically narrowed arteries: and cerebral and coronary thromboses have in fact been reported in conjunction with hexamethonium treatment. It is, however, difficult to decide how far the drug is responsible for these.

Hexamethonium salts can be given orally or by subcutaneous, intramuscular, or intravenous injection. They are poorly and irregularly absorbed by the gut, and the effective dose by mouth is at least ten times the parenteral dose. When they are administered by mouth the dose of anion may be important, and care should be taken if the bromide is used. The subcutaneous route is preferable. The drug is not metabolised in the body; normally it is rapidly excreted, but in the presence of renal failure small doses may produce long-continued effects. In uræmia, too, lowering the blood-pressure may further impair renal function, although no such effect is seen in uncomplicated hypertension.

The appropriate dose is a matter for careful trial in each case. As little as 25 mg. per day may be too much in a case with renal failure, whereas in hypertensives with good renal function as much as 250 mg. subcutaneously thrice daily may be needed. Tolerance to the drug may occur at first, especially when it is given by mouth. Patients should be admitted to hospital for the initial assessment of dosage, which is based on the results of repeated readings of the blood-pressure in the lying and standing positions and preferably some 2–3 hours after the test injection. The first dose is usually 25 mg. intravenously or intramuscularly, and then this or a larger dose is given two or three times a day. 'Methedrine' or adrenaline is kept at hand to treat any too dramatic fall in pressure, but is very seldom required. Once established, the effective dose will need occasional checking, which can be done at intervals during a day in the outpatient department. The aim is, not to produce a low pressure or postural hypotension throughout the 24 hours, but to restore full lability of the blood-pressure with three injections a day.

This is at best a difficult line of treatment, requiring rigorous supervision, and is not recommended for mild cases of hypertension. In the severe hypertensive with a bad prognosis the treatment is fully justified and very useful. Headaches, dyspnœa, and dizziness are almost invariably improved, and are thus indications for treatment. Once headaches and dizziness are relieved they may not recur for a long time, even if the treatment is discontinued. In both essential and renal hypertension, papillœdema and vision may be markedly improved, and so may vomiting and pulmonary and cerebral œdema. In severe hypertension continued regular treatment can undoubtedly prolong life. Professor Rosenheim concluded by emphasising that hexamethonium treatment is still experimental and has the disadvantage of causing parasympatholytic side-effects. The ideal drug should be absorbed regularly when given by mouth, or be long acting when injected. Despite the difficulties, hexamethonium has already proved very valuable in the treatment of severe hypertension.

Dr. Ralph Kauntze dealt with the use of the veratrum alkaloids in the treatment of hypertension. Although veratrum viride has been used sporadically in the treatment of eclampsia, uniform preparations of it were scarce until 'Veriloid' became available eighteen months ago. This preparation contains a stable and reproducible mixture of esters, and is standardised by bio-assay in dogs. Only a few pure alkaloids have so far been isolated, but these seem to produce as many side-effects as veriloid itself. The main effects are hypotension, bradycardia, and emesis. The action is both vagal and central, producing dilatation of arterioles in the skin and muscles with constriction of veins. The blood-pressure falls before bradycardia occurs, and is therefore independent of this, although it is reasonable to suppose that the slowing of the heart contributes to the hypotensive effect. Intravenous administration is more effective than oral, and about 1 μg. per kg. body-weight is the usual intravenous dose. Oral therapy leads to irregular absorption, and side-effects are harder to avoid. On a fasting stomach effect is maximal in 3–5 hours; food hastens absorption and it is therefore recommended that the drug should be taken after meals. Two doses a day can control the blood-pressure for 10 hours. For more complete control it should be taken every $4^1/_2$ hours in the day, and the last dose should be at 10 P.M. or later. The largest doses are given after breakfast and on retiring.

Toxic side-effects consist in a burning or empty feeling behind the lower part of the sternum, salivation, choking, hiccup, recurrent vomiting, coldness, and collapse. 12 mg. and upwards causes these effects, but the threshold may be raised by a small dose of phenobarbitone. Hypotension is effectively countered by ephedrine intramuscularly. If urticaria develops, both the veriloid and phenobarbitone should be temporarily omitted. Largely on account of the numerous potential side-effects it is best to have the patient in hospital until stabilised on veriloid and phenobarbitone, and after 3–4 weeks it may be necessary to lower the dosage. However, there is a tendency when the patient is back at full work for the blood-pressure to rise.

Over the last 18 months 23 patients have been treated —15 with benign essential hypertension, 5 with renal hypertension, and 3 with malignant hypertension. No patients were started on treatment unless the diastolic pressure exceeded 120 mm. Hg. Good results have been obtained in 6 cases, and fair or temporary improvement in about half of the total; but no attempt has been made to attain normal blood-pressures. The disease has progressed, but possibly more slowly than it otherwise would have. Headaches, dyspnœa, encephalopathic attacks, cerebral function, fundus changes, and triple rhythm have all improved or recovered under treatment; but the electrocardiographic appearances have not returned completely to normal. Since the drug is not sympatholytic postural hypotension does not occur except with very large doses. The fall in blood-pressure does not seem to impair kidney function, but 2 cerebral thromboses and 2 cerebral hæmorrhages have occurred under treatment. Intravenous veriloid can be relied on to lower the blood-pressure in all cases of hypertension, except in the pre-terminal malignant phase and possibly when there is a chromaffinoma. About 60% of cases respond to oral treatment, and in 20–30% excellent results can be obtained; but the therapeutic and toxic doses are very close. The therapeutic and toxic principles seem to be inseparable. Despite these drawbacks veriloid by mouth, in association with phenobarbitone to raise the threshold to nausea, and a sodium intake of less than 0·5 g. per day, is a practicable treatment, especially for the younger severe hypertensive.

Prof. J. McMICHAEL said that he had measured the cardiac output in normal men, hypertensives, and hypertensives receiving hexamethonium, in the recumbent and the standing or 30% head-up slant positions. In each of these groups there was a fall from about 4·8 to about 3 litres a minute in the latter positions, but those receiving hexamethonium fail to show the normal reflex vasoconstriction on standing. The hypotensive effect of this drug is therefore maximal when the patient is ambulant, rather than lying in bed. He, like Professor Rosenheim, holds that the drug should be given by the subcutaneous route about three times in the day. Of 7 malignant and pre-malignant hypertensives 4 remain well controlled after a year on hexamethonium; and of 27 less severe essential and rena hypertensives 18 are doing well. Professor McMichae agreed with Professor Rosenheim that hexamethonium should not be given for mild hypertension.

Professor ROSENHEIM felt that hexamethonium treatment should be continued indefinitely in suitable cases; and he had 1 patient still under good control afte 15 months' regular therapy. He had not observe coronary thrombosis during hexamethonium treatment but he felt that severe electrocardiographic change might be a contra-indication to its use. The time wa not yet ripe to compare the advantages of thoracolumba sympathectomy with those of hexamethonium, bu surgery was undoubtedly less of a trial for both patien and doctor.

Dr. KAUNTZE said that he would recommend surgery only for unilateral renal disease, when a sympathectomy could be performed at the same time, or in cases wher continuity of medical treatment was impossible.

Reviews of Books

Essays in Surgery

Editors: R. I. HARRIS and R. M. JANES. Toronto: University Press. London: Oxford University Press. 1951. Pp. 584. 75s.

William Edward Gallie possesses that very rare combination, originality and a gift for organisation. He has not only made lasting contributions to surgical science but has promoted the training of surgeons to such good purpose that Canadian surgery is second to none in the world. It was natural and seemly that his colleagues should pay him a tribute on his retiring from the chair of surgery in Toronto; and this volume is a symposium of the work of his colleagues and pupils. It is a tribute to the master that these are real contributions to surgery; they come from a group of active, vital, and practical men. That on the treatment of cleft palate presents the problems clearly and discusses them with authority, and there are informative papers on such common things as hernia, fractures of the os calcis, and bronchiectasis. But there are also papers on such recent advances as leucotomy for pain relief, hyperinsulinism, and chromaffinoma of the adrenals. There is a good article on bone-grafting the jaws after resection for malignant disease, but the crucial matter of the prospect of cure of the cancer by such resections is evaded. How many and what patients survive for any length of time after these removals? That is what we need to know before embarking on bone-grafting. But taking it all round, this collection of essays is about as good as it could be, particularly for the general surgeon.

Ocular Toxoplasmosis

M. J. HOGAN, associate clinical professor of ophthalmology, University of California Medical School. New York: Columbia University Press. London: Oxford University Press. 1951. Pp. 86. 18s.

This is a useful summary of information about toxoplasmosis as it affects the eye during intra-uterine life. Professor Hogan describes the histology of typical retinitis or chorioretinitis in the macular region, and gives an account of the investigation of cases of uveitis. When toxoplasmosis was produced in rabbits by injecting parasites into the carotid artery the uveal tract was chiefly involved. Other chapters deal with laboratory methods of diagnosis and the results of treating experimentally infected animals. There is also a valuable list of the main findings in 78 proved cases of the disease.

British Encyclopædia of Medical Practice (2nd ed London: Butterworth Medical Publications. 1952. Vol. Pp. 617. 65s.).—The alphabetical arrangement chosen by th editors takes the latest volume over a range which include no large section on any one subject. The first article is th longest—48 beautifully illustrated pages on mouth disease by Mr. E. Stanley Lee. The last is among the shortest—2 pages on pinta, the spotted sickness, by Dr. Sydne Thomson. Dr. W. M. Levitt contributes a cautionary not on professional negligence, but surely no doctor who ha this encyclopædia on his shelves need be afraid of tha charge.

Physiology of the Newborn Infant (2nd ed. Illinois Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1951. Pp. 348. 55s.).—Prof. Clement A. Smith ha made a unique and valuable contribution in reviewing th present state of knowledge about the physiology of the newborn infant. Thi edition, published six years after the first contains much new material. It is intended for active clinicians and as a reference book in pædiatrics and public health Only a dullard will be content to read the text withou wishing to explore some of the original papers; and here th comprehensive bibliography is helpful. Useful tables, an summarised reports from different sources, encourage th reader to assess the evidence for himself.

The book, which should be read in sequence, deals in tur with respiration, the circulation, the blood, metabolism an heat regulation, digestion and nutrition, renal physiolog and regulation of water and electrolytes, neonatal endocrinology. and neonatal immunology. The nervous system ha been omitted since available knowledge is inadequate for th writer's purpose. This is to describe the physiological processe in the fœtus and young infant, to draw conclusions about adaptation to environment, and to relate these to clinica problems commonly met in the neonatal period. Professo Smith is specially at home with respiration, on which he has himself made useful observations. In the chapters on metabolism, nutrition, and renal physiology, the emphasis on practical implications is on the whole somewhat forced—though there are some outstanding examples of clinical benefit deriving from the physiological approach. Thus the observation that tetany in newborn infants usually develops in those fed on cow's milk is related to the facts that cow's milk has a low calcium-phosphorus ratio and high phosphorus content as compared with human milk, and that at this age the infant excretes little phosphorus.

The book should be read in a reflective mood rather than in examination fever; and it will be wasted on those who try to use the clinical summaries as a guide to emergency treatment without an understanding of the full text. An unusual and somewhat ponderous style of writing is amply compensated for by the selection of material. and the way in which it is presented and discussed.

THE LANCET
LONDON: SATURDAY, MARCH 8, 1952

General Practice in the Curriculum

"If you do not demand complete responsibility, if you have no interest in original work, and if you have plenty of energy, I should not think that a general practice would be without its rewards."

"First, one must choose an under-doctored area. This is my most important point, for the doctor must be able to dispose of patients who are just a nuisance."

THESE remarkable statements—the first from a tudent, the second from a young doctor—appeared a symposium in a hospital journal last year, and re among the reasons why the writers felt that eneral practice was not for them. Nothing could emonstrate more strikingly how much our students eed, during their training, some instruction in he meaning, purposes, and responsibilities of general ractice; or how little some of them are aware f this need. The first writer evidently had no onception of the heavy responsibility carried by eneral practitioners, both in the preliminary sifting f cases and in the day-to-day guidance of patients, not only through some immediate disorder but through the strains and stresses, differing at every age, of life itself. He fancied, too, that "original" work is only done in the hospital or laboratory, not understanding that the doctor who notices some recurrent pattern in an epidemic, or in the ailments of an individual or a group, or who invents some device to ease or mobilise a patient, or who plans a better way of running his surgery, is engaged in original work, even if he does not write to the medical journals about it. The young doctor responsible for the second quotation seems to make the strange assumption that any patient of whom the doctor has "disposed" ceases, in some mysterious way, to exist. Someone has to take responsibility for him, however; and the right person to do it is his general practitioner. This, in fact, is one of the many responsibilities from which the good family doctor does not shy away.

Students and newly qualified doctors are not to be blamed for ignorant assertions of these kinds; they have had, as a rule, no chance to learn better. The fault lies in our teachers, many of whom still do not recognise their duty to prepare young doctors for the work in which three-quarters of them will pass their lives. It is a dangerous piece of neglect; for the level of work done by general practitioners in after life depends only partly on the standards learnt in hospital. Other factors carry more weight, and are apt to prove determinants. Is the young doctor modest and teachable, with a respect for mature opinion, and little self-regard? These qualities are good, and made him a splendid student; but they may also make him corruptible. If he goes into practice where standards are low, equipment poor, work rushed and scamped, he will of course recognise a great decline from hospital standards; "but," he may say, "they told me general practice would be very different: no doubt this is what they meant. I shall have to get used to it." And he sets himself to fit in with a type of work which he sees is poor but which he believes to be inevitable. In this way his very modesty and deference commit him to bad habits. Or again he may be ambitious and determined to make money; and ambition is no bad driving force if properly directed. But he may fall in with a senior in whom the urge to get on is altogether too well developed, and learn from him to put the patients' welfare some way behind his own advantage and convenience. He had suspected general practice was like this, and so it is; well, what of it? Nobody at his hospital had taught him to think more highly of it, or of himself. The standards he encounters can vary enormously, as the Collings report showed.[1] Bad quarters, insufficient equipment, poor lighting, lazy methods, failure to examine, are still commonplaces of general practice, and apt to be self-perpetuating. Moreover, the work is often hard—so hard that the extra energy needed for reform cannot be whipped up. He postpones, submits, gives in.

One or two hospitals are beginning to see their duty to their students more clearly; and a shining example is St. Mary's, Paddington, which for seventeen years has allowed a general practitioner to lecture on his subject to the students in the school.[2] The scheme started because a country general practitioner saw clearly, after five years in practice, that his hospital had not taught him the things young doctors need to know before they start; and because he believed that any young doctor of character, if he was shown a good standard at the outset, would never afterwards be content with a lower one. Over the years the little course he devised has taken a definite shape. He gives some half-dozen lectures at the hospital, at which attendance is optional; and as a rule the whole final year turns up. His aim is to show the students how to adapt their hospital training to the conditions in which they are going to work; how to discipline themselves and their lives to cope with it; how to work with partners, secretaries, and dispensers; how to arrange rota systems; what will be their relationship with the medical officer of health, the health visitors, the district nurses, the mental health officer and others; what is the least they will need in the way of surgery space and equipment; and what the book-work and certificates entail. At one of these lectures he tips out on to the table the contents of his daily bag and his midder bag, to show them the sort of equipment he has found useful on his rounds. Each of the objects, naturally, recalls an anecdote which helps to stamp the mental picture on the memory of the listeners. The lectures are given in the summer term to those approaching finals; their last three months are kept purposely clear of other training commitments, and they come to the lectures with minds disposed to make the best of the opportunity. Then on a Sunday afternoon, the doctor receives a bus load of 30–40 students at his surgery.

His country practice lies in beautiful surroundings, which makes the visit pleasant in any case; but it is also exceptionally well housed, well equipped, and well

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1. *Lancet*, 1950, i, 555.
2. *Ibid*, ii, 689.

run, and it sets the young people thinking on new lines about general practice. To meet the students there are the doctor's wife, his secretary and dispenser, any *neighbouring general practitioners and their wives* who can get along, all six of the local district nurses, the health visitor, the medical officer of health, the "duly authorised officer" of the local authority, and usually someone senior from one of the teaching hospitals, curious to see what is going on. The students are encouraged to bring any "wives, fiancées or attachments who want to talk about the doctor's wife's side." They examine every inch of the double surgery, waiting-room (with rocking-horse), dispensary, and locum's bedroom, and ask as many questions as they like, both then and later at tea.

This used to complete the course on general practice: six lectures and an afternoon visit. But feeling, perhaps, that as a preparation for real life this compared somewhat slightly with six months' attendance in the operating-theatre, the lecturer, during the last year or two, has arranged for students to spend a full week "sitting in" on a practice, seeing what comes, discussing cases and methods, and talking to patients in their homes. He himself takes one student for a week every two or three months; and through the Nuffield Provincial Hospitals Trust he has been able to get into touch with a number of first-rate general practitioners who work in every kind of social environment up and down the country. Twelve of these are now taking three or four students each for a week at a time, spaced over the year. The student lives in a local public-house, or in rooms, and spends his days with the doctor, sitting in during surgery, going on his rounds, and accompanying him into the houses. The patients seem to like it; and the doctor often finds that the fresh outlook and news of recent advances outweigh, for him, the extra work entailed. Moreover the presence of the young person smartly checks any tendency to fall into slipshod methods.

The visit is usually arranged during the last months before the student's finals. He is sent to the kind of practice in which he hopes to settle down, and St. Mary's allows him a small sum to cover his expenses. Meetings are now being arranged between the dean of the medical school, the practitioners accepting students, and the students who have done a week in a practice, to discuss ways of making the scheme more practical and helpful.

On much the same lines as Dr. GEOFFREY BARBER, the originator of this scheme, Dr. E. M. DIMOCK and his partner, Dr. J. L. D. ROBERTS, have started a scheme for University College Hospital. Here the student is invited to stay from Monday at 5 P.M. to Saturday midday. On arrival he is received at the surgery by the nurse-secretary, who shows him the surgery accommodation and equipment, and demonstrates general-practice methods for such things as sterilising. After attending surgery and accompanying the doctor on any emergency visits, he spends the evening at the doctor's house in a preliminary discussion. On the following days he attends surgery, joins in visits, goes to the infant-welfare centre, the antenatal clinic, or whatever is scheduled for the day, and spends his evenings, like the first, in discussion. On Friday morning he is given a case to write up from the general practitioner's viewpoint, and his last evening is spent in discussing this. Dr. DIMOCK's practice is in a residential rural district, and he and his partner have separate surgeries in a single-storey building designed and built for the purpose. Here again the student has the chance of seeing a really well-housed well-run practice, and of acquiring standards that will prevent him, ever after, being satisfied with the second-rate. Plans are being *made to give talks at University College* Ho to final-year students on aspects of general practi and, like St. Mary's, University College Hospital ho to arrange with doctors in other types of practice accept students. Dr. DIMOCK intends to align content of the talks with the teaching of the s at the hospital, so that students will see how t training can be maintained, extended, and adapted use in general practice.

These are two admirable schemes, and we shall glad to hear what others are in operation. We h been told, for example, of one medical school wh arranges for a general practitioner to attend w rounds: after demonstrating a case the consult taking the round asks the practitioner to disc any points of special interest to him; and it is th apparently, that particularly interest the studen The idea of teaching general practice is, of cou by no means new, and some schemes have been *operation for a long time—notably the* "*dispensar* system in Scottish universities.[3] Nevertheless inte in this important aspect of medical training h on the whole, been desultory, and it is high ti more of the teaching hospitals offered adequ courses.

Radio-iodine *versus* B.M.R.

IN this age of rapid progress it is as well to reminded that the newest diagnostic procedures *not necessarily the best. Such reminders are parti* larly needed with methods imported into medic from atomic physics, as in the case of radioact isotopes. By means of the Geiger counter the pera bulations through the body of atoms labelled in t way can be accurately followed even though th have been administered in fantastically small dos The elegance of the technique sometimes leads unwary to assume that any clinical test with isoto will give the desired information. In fact such te need to be assessed in exactly the same criti spirit as any other diagnostic procedure. In a let published in this issue, Dr. ROBERTSON gives his o opinion of the value of radio-iodine tests in the di nosis of thyroid disease, and compares these to th detriment with the older method of measurement the basal metabolic rate (B.M.R.). His critical co servatism should be a valuable corrective for th carried away by the glamour of modern aton physics, and his arguments certainly deserve care study.

Dr. ROBERTSON's thesis is derived mainly fr studies by KEATING and others[4] at the Ma clinic, and by WAYNE and his colleagues[5] in Sheffie Both these articles were mainly concerned with detailed comparison of the diagnostic efficiency various methods of assessing iodine metabolism wi the help of the radioactive isotope, I^{131}; and mo or less incidentally both articles give figures for t B.M.R.s of the patients who were studied. The figures have been abstracted by Dr. ROBERTSON a compared with the values for the rate of radio-iodi uptake. Viewed in this way the results of the t nvestigations are apparently contradictory. At the Mayo Clinic the B.M.R. gave a higher proportion of correct diagnosis (in both hyperthyroidism and hypothyroidism) than measurement of radio-iodine uptake; whereas at Sheffield the B.M.R. was much less informative than the radio-iodine tests. But the wide range of normality cited by the Sheffield group for their B.M.R. measurements leads Dr. Robertson to suspect their technique. His own large experience has made him distrustful of claims that hyperthyroidism can be present in patients with a normal B.M.R., except rarely in those whose metabolic rate was in the lower range of normal before they contracted the disease. With this conclusion most will agree; those who distrust the B.M.R. usually do so less because it often fails to confirm frank hyperthyroidism than because results above the range of normality are found in many euthyroid subjects. The B.M.R. measures hypermetabolism, not hyperthyroidism; and the two are by no means synonymous. Dr. Robertson contends that it is the clinician's job to exclude non-thyroid causes of hypermetabolism. For the patient in heart-failure with suspected hyperthyroidism he adopts the somewhat clumsy expedient of measuring the B.M.R. before and after a course of iodine; since the patient's cardiac condition may have improved in the interval, a fall in the B.M.R. after iodine treatment is not necessarily conclusive. But the most important practical difficulty of all is in achieving a satisfactory measurement of the B.M.R. in an anxious patient—and most patients suspected of hyperthyroidism are anxious. This raises a problem to which the majority of clinics have been unable to find a satisfactory solution. Dr. Robertson maintains, however, that basal conditions can always be obtained "with patience." This implies that the observed result cannot be wholly objective; it contains also the operator's subjective opinion that the patient was truly basal at the time of the test. Others have concluded that the B.M.R. gives satisfactory results only in anæsthetised patients.[6 7]

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[3] Scott, R. *Ibid*, p. 695.

[4] Keating, F. R., Haines, S. F., Power, M. H., Williams, M. M. *J. clin. Endocrinol.* 1950, 10, 1425.

[5] Goodwin, J. F., Macgregor, A. G., Miller, H., Wayne, E. *Quart. J. Med.* 1951 20, 353.

Radio-iodine tests do not have these disadvantages. The Geiger counter is not called on to exercise judgment, and the counts it records will be the same whether the patient dislikes the test or not; and disease in other parts of the body will affect these tests only if the thyroid itself is affected. But though these tests indicate disturbance of thyroid function they do not necessarily do so in terms that are clinically helpful. Some non-toxic goitres take up radio-iodine at a higher rate than normal, and so do the thyroids of some patients who have fully recovered from hyperthyroidism. The test correctly states that these subjects have abnormal thyroids, but it does not say whether the abnormality is clinically significant, and in fact cannot discriminate between frank hyperthyroidism and other abnormalities. Moreover the test is liable to be upset by the ingestion of iodides or antithyroid substances in the diet. A herring for breakfast, or a dish of turnips for lunch, might easily cause confusing results. Possibly even more serious, we do not know the extent of day-to-day or hour-to-hour fluctuations in thyroid function. Such fluctuations would not affect the B.M.R., which is sensitive only to long-term changes in thyroxine output; but they might well be important when the test lasts only an hour or two.

Both types of test have evident deficiencies, yet both undoubtedly give useful information about the state of thyroid function. Since the deficiencies are different in kind it might be thought that the two tests should be regarded as complementary. Such in fact is the conclusion reached from a careful comparison at the Westminster Hospital. In this investigation, which is published on an earlier page of this issue, Professor Maclagan and his colleagues demonstrated a clear correlation between B.M.R. and radio-iodine uptake in a large series of subjects with and without thyroid disease. In untreated cases of thyrotoxicosis the newer method appeared to give better guidance; but in certain situations—particularly during or after treatment with antithyroid drugs—the results could be very misleading. It is perhaps pertinent to remark that Dr. Robertson, while insisting on precise technique in measuring the B.M.R., appears to accept all radio-iodine techniques as equivalent. In fact the techniques are almost as numerous as the clinics which use radio-iodine in diagnosis. It is particularly important not to discourage the search for better methods, even if Dr. Robertson's strictures on those now in use are reasonable. It is unlikely that the techniques of the B.M.R. will be improved, but it is very probable that radio-iodine will be used more and more efficiently. Both the test described by Professor Wayne (measurement of protein-bound radioactivity 48 hours after a dose of I^{131}) and that used by Professor Maclagan (the thigh-neck clearance) are promising indications of progress. Both appear to be improvements on the measurement of 24-hour thyroid uptake at present widely used in America; and probably further refinements will be made before any one test is universally accepted.

While these developments should be encouraged, it is also important that radio-iodine and other isotopes should remain (as they are at present) in the hands of responsible investigators. As Dr. Robertson rightly says, the possible long-term effects on the thyroid of even tracer doses of radio-iodine have not yet been properly assessed. Although the calculated dose to the gland compares favourably with that received by the skin in many standard procedures of diagnostic radiology, much longer experience will be required before it can be said that no radiation hazard is involved. This means that radio-iodine tests cannot be repeated as often as may be clinically desirable. If there is a radiation hazard it must necessarily vary with the amount of radioactivity administered. Unfortunately both the new methods require doses of 30 μC of I^{131}, which is three times as much as that with the urinary output method.[8] Further research should be directed towards decreasing the patient's exposure to radiation as much as towards increasing the accuracy of the procedure. In this connection the most promising method seems to be that described by Stanley and Astwood,[9] and used in this country by Foss and Herbert.[10] The patient is given a preliminary dose of an antithyroid drug, large enough to prevent organic binding of iodine. The subsequent dose of I^{131} is concentrated by the thyroid in its

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[6] Bartels, E. C. *J. clin. Endocrinol.* 1949, 9, 1190.

[7] Rapport, R. L., Curtis, G. M., Simcox, S. J. *Ibid*, 1951, 11, 1549.

[8] Mason, A. S., Oliver, R. *Lancet*, 1949, ii, 456.

[9] Stanley, M. M., Astwood, E. B. *Endocrinol.* 1948, 42, 107.

[10] Foss, G. L., Herbert, R. *Clin. Sci.* 1952, 11, 33.

inorganic state, and the peak concentration measured after 1 or 2 hours. The radio-iodine is then discharged from the thyroid by giving thiocyanate, leaving the patient with a negligible amount of radioactivity in the gland. This method has the great merit of reducing the radiation hazard to very small proportions; but its reliability as a diagnostic measure needs to be further confirmed.

Contact Examination

TUBERCULOSIS workers agree that all household contacts should be examined as soon as possible after a case of pulmonary tuberculosis has been detected. The essentials are radiographic examination of the chest and a tuberculin test for those up to 15 years of age. After this initial examination the most useful procedure is less certain, especially with regard to the questions Which contacts ? How often ? For how long ? Dr. ASPIN's paper in this issue goes a long way, however, towards answering these questions, and its main conclusions agree remarkably with those of PUFFER and her colleagues,[1] whose report has just reached this country. Both these investigations are based on principles laid down many years ago by WADE HAMPTON FROST.

As Dr. ASPIN remarks, repeated examination of children of school age at one time formed a large part of routine contact examinations ; but his results and those of PUFFER et al. confirm that, after the first examination, the yield of cases from tuberculin-positive children aged 5–14 years is practically nil. The important procedure for this age-group is the tuberculin test ; and if negative, this should be followed by B.C.G. vaccination. There should, of course, be an initial radiographic examination, but if this shows nothing abnormal and the tuberculin test is positive, the child runs little risk until the age of puberty. Our habit of classifying age-groups as 0–4, 5–9, and 10–14 years may here lead us into danger ; the age at which the risk of tuberculosis increases is not so sharply defined, and—especially for those whose main source of infection is at home—probably does not depend mainly on leaving school. As PUFFER et al. suggest, the danger is associated with puberty ; and the special risk comes earlier in Negro children, in whom puberty is earlier. If 15 years were accepted as the age at which contact examination should be intensified, this would expose to unnecessary risk the considerable numbers in whom puberty begins much earlier ; this applies particularly to girls, and it is worth remembering that the menarche, though a conspicuous feature of puberty, is by no means its earliest manifestation.[2] In Dr. ASPIN's series at Leeds tuberculosis developed in no child aged 5–9 years, but it developed in 2 aged 10–14 years. In PUFFER's American series no case arose in white children aged 5–14 years, though 5 occurred in individuals aged 15 years or more who had been under observation when less than 15 years of age. There were 2 cases in Negro children aged 5–9 years, and 8 in the 10–14 age-group—4 of them aged 14 years. Both papers emphasise the very high attack-rate in people aged 15–34 years, and Dr. ASPIN shows also a very high yield in this group at the first examination ; both studies make it clear that at this age the risk is appreciably greater in females than in males. In later life the attack-rate is very much lower, and a little greater in men than women.

Thanks to very complete cross-referencing in the Leeds records, Dr. ASPIN was able, after a lapse of ten years, to relate his " index cases," notified between Jan. 1, 1938, and Aug. 31, 1939, to previous and subsequent cases notified from the same households. Among the 680 households nearly three out of four had no other known case of tuberculosis ; these index cases were isolated manifestations that could not have been revealed by any system of contact examination, and they underline the need for other methods of case-finding—especially reference of patients with symptoms by general practitioners, and mass radiography. In 20% of the families there had been a previous case, and in 10% a case was subsequently found ; these two groups overlapped slightly, for 3% of all families had both a previous and a subsequent case. Half the subsequent cases were notified within a year of the index case ; thereafter the yield fell until the sixth year, after which the incidence of new notifications was little, if any, higher than in the general population of Leeds. The very high incidence of notification in the first year cannot necessarily be interpreted as a high " attack-rate " in this year, since many of the cases were first examined in this period and the disease may have been present for some time. A similar consideration applies to the large number of previous cases in the year preceding notification of the index case. These very high figures are partly due to the method of analysis ; this presents a perfectly accurate picture of the amount of work involved for a given yield of cases, but from the epidemiological aspect the figures for these two years cannot be regarded as " attack-rates " and in this sense are not strictly comparable with the results for subsequent years. Dr. ASPIN also shows, *as have* other workers, that the incidence of *secondary* cases is greater among contacts of cases *with* a positive sputum than among contacts of cases in which the sputum has not been proved positive. The American paper deals only with the contacts of sputum-positive or fatal cases. The attack-rate is not analysed for separate years from the date of notification of the index case, but a declining yield in subsequent years is reflected by the falling attack-rates as the duration of the study increases. The attack-rate is, however, studied for race and degree of genetic relationship with the index case. For white people of either sex the attack-rate is higher among close relatives (parent, sibling, or child) than among other household associates. In the Negro group there is a similar but less distinct tendency for the incidence to be higher in close relatives, whose rates are considerably higher than for comparable white groups. All these results, based on attack-rates, are substantially confirmed by similar analyses based on mortality experience.

Taken together these two papers show once again the importance of familial contact, age, and sex as factors in the pathogenesis of tuberculosis. The American work illustrates, too, the importance of race and of genetic relationship with the established ase ; while the Leeds results indicate that a positive putum carries added risk to the household associates. t also indicates that the greatest return of new cases may be obtained by concentrating on those at greatest isk—close relatives in young adult life, especially emales, up to 5 years from cessation of contact. Dr. ASPIN concludes with a tribute to the health visitors and office staffs on whom falls the brunt of following-up contacts. Health visitors everywhere may take heart from his analyses, and proceed with renewed vigour to their often difficult task of persuading all contacts of the need for at least one examination, and to the even more difficult duty of persuading young adults to attend regularly for 5 years.

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[1] Puffer, R. R., Zeldberg, L. D., Dillon, A., Gass, R. S., Hutcheson, R. H. *Amer. Rev. Tuberc.* 1952, 65, 111.

[2] Hogben, H., Waterhouse, J. A. H., Hogben, L. *Brit. J. soc. Med.* 1948, 2, 29.

Annotations

A BIG STEP FORWARD

THOSE concerned with the financial affairs of hospitals will note with thankfulness the Minister of Health's decision[1] that regional hospital boards shall resume their power to approve the estimates of management committees and to sanction transfers between the authorised subgroups of expenditure. Though certainly made with the best intentions, the arrangement by which H.M.C. budgets and transfers between the subheads could be approved only by the Ministry was fundamentally unsound. Centralised control breaks down unless personal contact can be maintained, and with 374 management committees this was impossible. With direct Ministerial control, the H.M.C. finance officer, Mr. Honest John, lost every time, when his budget was cut; but Mr. Smart Alick saved himself and his committee from any discomfiture by anticipating and outwitting the Ministry, while keeping within the letter of the law. In practice, of course, Honest John and Smart Alick are often one and the same person, the Jekyll/Hyde ratio being determined by the administrative strains to which they are subjected ; but the system was certainly inimical to the development of the medical services where they are most needed. Under the new arrangement one regional finance officer will be related to some 20 or 30 H.M.C. finance officers, and personal contact will be assured. One may reasonably assume that considerable flexibility will be allowed by regional boards for transfer under different heads, depending on varying local conditions ; and, if there is enlightened regional control with flexibility, the H.M.C.s will in effect be receiving a block allocation which will greatly enhance their sense of financial responsibility. The revised system of control is psychologically sound and eminently practical, and the Ministry may congratulate itself on having at last succeeded in organising a financial system which will not inhibit the stimulus to economy. With this arrangement there is no reason why a board and its management committees should not develop the same kind of mutual trust and confidence as normally exists between a university and its constituent colleges.

This memorandum is also a welcome indication that the Ministry is deciding to increase rather than to decrease the functions of the regional boards. Nobody at the periphery can doubt that benefits would accrue from leaving the month-to-month decisions and the integration of the medical services to those who are fully informed of the local conditions. Relieved of such responsibilities, the Ministry could properly concentrate on national policies and the interrelation of the many medical services.

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[1] Circular R.H.B.(52)20, H.M.C.(52)19.

CHEMOTHERAPY OF TUBERCULOSIS

FOR fuller information about the use of nicotinic acid isomer derivatives in tuberculosis[1] we shall have to await the reports appearing (see p. 518) in the April issue of the *American Review of Tuberculosis*. Some of the more cautious statements about these preparations, however, have suggested that, even if they fulfil their present promise, they may supplement rather than supplant existing remedies. This would be in line with accepted teachings on the chemotherapy of tuberculosis ; for it has been held that, to be fully effective against this disease, a drug must be able to penetrate not only the tough waxy skin of the tubercle bacillus but also the tubercle, the tuberculous cavity, and finally the living cell in which the bacillus so often lies. The anatomical and chemical features of tuberculous lesions make this a complex problem, and have indeed suggested that a single substance embodying all the necessary properties might never be found.

Sir Howard Florey[2] recently analysed these technical difficulties and gave an account of enterprising attempts to overcome them in his laboratory at Oxford. One basic disadvantage shared by most drugs commonly used in the treatment of tuberculosis is that a substance which is effectively distributed in extravascular fluids, and even in caseous material, does not necessarily penetrate the mononuclear cells harbouring bacilli, and for this reason Florey and his colleagues began to examine "by a series of somewhat halting steps" the possibility of getting drugs into contact with intracellular bacilli. A research tool for this task was fortunately to hand in the shape of micrococcin, an antibiotic isolated by Su[3] from a species of micrococcus present in the Oxford sewage. Micrococcin actively inhibited a number of gram-positive organisms, including *Mycobacterium tuberculosis* ; but, unlike most tuberculostatic substances, it was virtually insoluble in water. In vitro, it became readily and irreversibly bound to growing, sensitive organisms, but not to insensitive organisms. The active substance fluoresced in ultraviolet light, and this property was used to trace its pathway in animal tissues : finely particulate micrococcin was taken up by macrophages, Kupffer cells, and other components of the reticulo-endothelial system without obvious damage to the cells. Other preliminary experiments, with carbon as a tracer, showed that particles of comparable size could enter tubercles in the early stages of infection. When injected into tuberculous animals, however, the micrococcin particles were aggregated by adherent platelets, failing thereby to gain effective access to the cells at the edge of tubercles, so that no real therapeutic action resulted. This difficulty was partly surmounted by injecting micrococcin brought into colloidal solution with a non-toxic detergent; but, although in this form it was taken up and retained by macrophages at the periphery of tubercles, it failed to enter the tubercles, and again there was no significant effect on the survival-time or development of lesions in the infected guineapigs.[4]

The failure of these ingenious experiments stimulated the Oxford workers to study isolated macrophages more closely, and Mackaness, using a technique recently demonstrated,[5] showed that colloidal micrococcin, in concentrations of 100 μg. per ml. of culture medium, was only able to retard the death of infected macrophages, whereas streptomycin, at 10 μg. per ml., inhibited the bacilli and preserved the life of the cells. Such a concentration of streptomycin is fully ten times that usually required to inhibit the growth of the free bacilli in liquid media. It is probable, therefore, that streptomycin would be a more useful drug if means could be found of maintaining concentrations as high as 10 μg. per ml. in the milieu of infected tissues. This might be achieved by local hyperæmia, which could explain the beneficial results observed by Smith and Vollum [6] in certain refractory cases of tuberculous meningitis after intrathecal injections of tuberculin. In general, it seems advantageous to investigate, as adjuvants to known or speculative antibacterial agents, other substances whose physical activity affects the lesions rather than the bacteria. A useful lead here is given by the work of Hart and his colleagues [7] who found that certain non-ionic, surface-active detergents inhibited the development of experimental tuberculosis in mice.

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[1] See *Lancet*, March 1, 1952, p. 454.

[2] Florey, H. W. *Proc. R. Soc. Med.* 1952, 45, 71.

[3] Su, T. L. *Brit. J. exp. Path.* 1948, 29, 473.

[4] Markham, N. P., Florey, H. W., Heatley, N. G., Saunders, A. G., Wells, A. Q. *Ibid.* 1951, 32, 25, 136, 353, 452.

[5] Mackaness, G. B. Demonstration to Pathological Society of Great Britain and Ireland. Cambridge, January, 1952.

In tuberculosis, moreover, the body's own defences are considerable, and there is experimental evidence [8] to suggest that a drug such as streptomycin is active by reason of its ability to attenuate the virulence of infecting bacilli, or reduce their numbers to levels at which the host's resistance, natural or gradually acquired, becomes dominant.

On the pharmaceutical rather than antibiotic front, mention may be made of a new sulphone derivative—α-amino butanoic γ-methyl sulphone (191 RB)—prepared by Brazilian workers [9] and found active against tuberculosis in the guineapig. Biochemically this compound is interesting because it is an oxidation product of methionine, one of the essential amino-acids containing sulphur and a precursor of glutathione. In laboratory animals 191 RB has a low degree of toxicity; and in a daily dose of 0·5 mg. per kg. body-weight it increases the survival-rate of guineapigs infected with the H37RV strain of tubercle bacillus. The other sulphones give good results in animals infected with tuberculosis, but they are of little value in man; and this may also be true of 191 RB. A trial in leprosy would, however, be worth while.

In Dublin Barry and McNally,[10] working under the auspices of the Medical Research Council of Ireland, have prepared two new compounds with tuberculostatic action that are chemically unrelated to the sulphones. These compounds have been given the code names B52 and B283. The first of these, B52, is the sodium salt of the mixed isomeric monoethyl esters of α-methyl-α′-*n*-dodecyl succinic acid. It inhibits the growth of the human strain of *Myco. tuberculosis* at a dilution of 1 in 200,000 to 1 in 400,000 in nutrient broth; but its activity is considerably reduced in the presence of human serum.[11] The drug produces a significant reduction in the lesions of pulmonary tuberculosis in guineapigs.[12] Limited clinical trials have been carried out. Corrigan,[13] of Harefield Sanatorium, Middlesex, suggests that it is of some value when applied locally to tuberculous sinuses, although it was disappointing in the treatment of tuberculous empyemata. Lane,[14] at the Meath Hospital, Dublin, reported that it was highly successful in the treatment of tuberculous lesions of the bladder. Despite its high tuberculostatic activity in vitro, B52 is unlikely to prove of general value, because its activity is greatly reduced by serum. Moreover, when injected intramuscularly it causes local destruction, and when given intravenously it can produce thrombophlebitis and hæmolysis.

B283, which is the hydrochloride of 2-anilino-3-imino-5-phenylphenazine, is a dark red pigment that inhibits the growth of *Myco. tuberculosis* H37RV at a dilution of 1 in 5 million.[15] It suppresses tuberculous infection in mice and guineapigs when administered at a dose level of 400 mg. per kg. body-weight daily, which corresponds to about 14 g. for a human being. Lane [14] claims that in a small series of patients with renal tuberculosis the conversion-rate approximated to that obtained with streptomycin. Unfortunately, however, the relapse-rate is high; and the drug colours the skin bright red, and has several undesirable side-effects such as nausea, vomiting, loss of weight, dermatitis, and jaundice. Nevertheless Barnes and Allday [16] have reported from Nigeria clinical improvement in cases of lepromatous leprosy treated with 500 mg. of B283 daily.

THE BILL FOR GUARDING FIRES

GAS and electric fires—cheap to buy, convenient to use, warm in a moment—are a benign invention in every way but one; and exactly the same praise and blame apply to raised cotton fabrics. Between them, these three are responsible for a large proportion of the burns, especially of children and old people, treated every year in our hospitals. Dr. Leonard Colebrook, F.R.S., and Mrs. Vera Colebrook, whose painstaking studies of burns and scalds due to accidents in the home have shown us the way to prevention, estimate that some 17,500 burned or scalded people are admitted to hospital each year, and that at least 1000 of the accidents are associated with unguarded gas or electric fires. Young children make up nearly three-quarters of the cases; and the commonest accident is for the raised cotton nightgown to touch an unguarded fire, whether gas, electric, or coal. A simple way of preventing many of the accidents would be to fit all fires with adequate guards, and Dr. Colebrook has been working for some years to get the sale of unguarded gas and electric fires made illegal. Last year the British Standards Institution issued safety specifications for these fires.

On March 14, a Private Member's Bill to forbid the sale of such fires without an effective guard is coming up for a second reading. It was first presented by Mr. D. G. Bullard, M.P., last December. Dr. Colebrook has, of course, taken great interest in the launching of the Bill, which certainly deserves a favourable hearing. Should it be passed, compulsory guards, it is hoped, will be an integral part of these fires, and penalties will be imposed for offering unguarded fires for sale. The present shortage of metal may, it is feared, at first hinder the production of guarded fires, and so lead to a fall in the numbers produced. But if national defence is to be the criterion, here is a form of defence on which we ought to have been spending money for years.

CORNEAL GRAFTING

BETWEEN the two world wars corneal grafting was usually carried out by opening the eyeball and inserting a full-thickness graft. The usefulness of this procedure was, however, limited by the high incidence of complications and the uncertainty of permanent visual improvement. An alternative method, which has been revived by French and Swiss ophthalmic surgeons, consists in the application of partial-thickness or lamellar grafts. This technique is much safer, since the globe is not opened; and with its introduction the indications for grafting have greatly increased. Lamellar keratoplasty is suitable not only for restoring sight where blindness is due entirely to corneal scars: it is also valuable for the actual treatment of active corneal ulceration, intertial keratitis, and recurrent pterygium. This method nefits about 70% of cases of corneal scarring; but deep scars, such as those of disciform keratitis, scemetocele, and conical cornea, a penetration graft mains the method of choice.

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[6] Smith, H. V., Vollum, R. L. *Lancet*, 1950, ii, 275.
[7] Cornforth, J. W., Hart, P. D'A., Rees, R. J. W., Stock, J. A. *Nature, Lond.* 1951, 168, 150.
[8] Martin, A. R., Stewart, G. T. *Brit. J. exp. Path.* 1950, 31, 189.
[9] Ramounoulou, A., Mors, B. *Publ. méd., S. Paulo*, 1950, 21, 21.
[10] Barry, V. C., McNally, P. A. *Nature, Lond.* 1945, 156, 48.
[11] McNally, P. A. *Brit. J. exp. Path.* 1947, 26, 161.
[12] Barry, V. C., Belton, J. G., Kelly, R. M., Twomey, D. *Nature, Lond.* 1950, 166, 303.
[13] Corrigan, F. Cited by Conalty, M. L. *Tubercle*, 1951, 32, 263.
[14] Lane, T. J. D. *Irish J. med. Sci.* 1951, 309, 393.
[15] Barry, V. C., Belton, J. G., Conalty, M. L., Twomey, D. *Nature, Lond.* 1948, 162, 622.
[16] Barnes, J., Allday, E. Cited by Conalty, M. L. *Tubercle*, 1951, 32, 263.

Formerly enough donor material was obtained from es excised for disease of the posterior eye, such as oroidal sarcoma, or because of injury. Now, however, ch material no longer suffices both because the dications for grafting have been extended, and also ecause larger grafts are now used: whereas full-thick-ss grafts are usually some 5 mm. in diameter, lamellar afts are 8–10 mm. Fœtal, animal, and inorganic grafts e useless. The best source is the cadaver of an aged erson who has died from natural causes, and from hich the eye has been removed less than two hours fter death. At present the law does not allow of this rocedure.

In France donor eyes have been made available by ecree; and in this country a motion on the order aper of the House of Commons seeks to clarify the law nd to increase donor supplies by voluntary means. he amendment is expected to deal with the bequest f eyes, and the use of eyes of people who have died n hospital where no previous objection to the procedure as been expressed and where the relatives agree. In is letter on another page, Sir Cecil Wakeley expresses he hope that Parliament will approve this measure, hich would do much to aid the treatment of patients linded by corneal disease.

MURRAY VALLEY ENCEPHALITIS

A YEAR ago encephalitis broke out in the Murray Valley of Northern Victoria and New South Wales; there were 40 severe cases, with 17 deaths. The outbreak attracted a good deal of public interest in Australia, particularly because it began soon after an epizootic of infectious myxomatosis had been purposely established in rabbits along the Murray river, thus arousing suspicion that the cases were related to the myxoma virus. An extensive series of investigations was therefore planned to elucidate the aetiology of the outbreak; and these have now been completed.[1–5]

The cause of the outbreak was established by recovering from 3 cases strains of a neurotropic virus allied to, but not identical with, the Japanese encephalitis B virus. French[2] records that this was first isolated from the brain of a fatal case by inoculating the chorio-allantoic membrane of fertile hens' eggs. After several egg passages it proved possible to infect mice intracerebrally, and in these the picture was typical of a neurotropic virus infection. Guineapigs and rabbits could not be infected, though they developed complement-fixing and neutralising antibodies after injection with egg or mouse virus. The organism was shown to be serologically related to Japanese encephalitis B virus by both complement fixation and neutralisation tests; the neutralisation tests were performed by intraperitoneal inoculation of baby mice.

The clinical picture is described by Robertson and McLorinan.[3] Those affected ranged in age from a few months to 70 years; the mildest cases were not clinically distinctive, but in the severe cases the picture was clear-cut. Headache, fever, and drowsiness were followed by disordered consciousness; and stiff neck, involuntary movements, upper and lower motor neurone paralysis, and coma and death from bulbar paralysis were all seen. The cerebrospinal fluid showed pleocytosis with a predominantly lymphocytic exudate. The brain was generally involved, with necrosis of neurones particularly in the thalamus and brain-stem.[4] A striking reduction in the number of Purkinje cells in the cerebellum, diffuse cellular infiltration of the grey matter of the brain and cord, and loss of anterior horn cells of the cord were also observed. The morbid anatomy resembled that of Japanese B encephalitis, and also recalled the condition found in the 1917–18 outbreaks (Australian X disease).

Probably the most interesting of all the results are those of a survey, by Anderson et al.,[5] of sera from various parts of Australia. Complement-fixing antibodies to the virus of Murray Valley encephalitis virus were sought and found in sera from many parts of Eastern Australia, though the highest percentages of positive results were obtained in Northern Victoria, the town of Cairns, Queensland, and New Guinea. Anderson concludes that as sera from healthy people are positive the virus infection is often subclinical. Indeed, he estimates a ratio of seven hundred subclinical infections to one case of encephalitis.

The reservoir of infection and mode of spread have not yet been worked out, but in sera from wild birds in the Murray Valley there was a high incidence of antibodies, as in the case of Western equine and St. Louis encephalitis in the U.S.A. Horses and dogs, but not sheep or cattle, also yielded serological evidence of infection. Clearly the virus must be recovered in the field before the natural cycle of infection can be known, but the bird-mite reservoir has been well substantiated in the U.S.A. by much careful work on arthropod-borne virus encephalitis.[6] A similar avian reservoir for Japanese encephalitis B virus is suggested by recent American work in Japan.[7] From this reservoir mosquitoes carry the infection to man, so that the human infection is a "spill-over" of virus from its natural avian habitat. Such a formidable virus reservoir presents a public-health problem which has not yet been solved; indeed American workers are frankly pessimistic.[8] Burnet[9] wonders whether the problem of encephalitis in man relative to the extent of subclinical natural infection is large enough to be significant. In Australia much depends on whether the encephalitis returns this year and next, or whether a long gap ensues. If, as seems probable, the virus of Australian X disease (the encephalitis of 1917 and 1918) is the same as that of 1951, long pauses in natural epidemicity in man seem likely.

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1. Anderson, S. G. *Med. J. Aust.* Jan. 26, 1952, p. 97.
2. French, E. L. *Ibid*, p. 100.
3. Robertson, E. G., McLorinan, H. *Ibid*, p. 103.
4. Robertson, E. G. *Ibid*, p. 107.
5. Anderson, S. G., Donnelley, M., Stevenson, W. J., Caldwell, N. J., Eagle, M. *Ibid*, p. 110.
6. Hammon, W. McD. *Amer. J. trop. Med.* 1948, 28, 515.
7. Hammond, W., Reeves, W. C., Sathers, G. E. *Amer. J. Hyg.* 1951, 53, 249.
8. Reeves, W. C. *Amer. J. publ. Hlth*, 1951, 41, 678.
9. Burnet, F. M. *Med. J. Aust.* Feb. 9, 1952, p. 169.

DR. J. A. SCOTT has been appointed medical officer of health and school medical officer of the County of London in succession to Sir Allen Daley, who retired last month.

ON Wednesday, March 12, at 10.30 A.M., in the Chancery Division of the Law Courts, London, W.C.2, the adjudication on the remuneration of general practitioners will be opened before Mr. Justice Danckwerts.

Sir JOSEPH SKEVINGTON, formerly senior surgeon to King Edward VII Hospital, Windsor, died on Feb. 29 at the age of 79. He was appointed K.C.V.O. in 1919.

THE INDEX and title-page to Vol. II, 1951, which was completed with THE LANCET of Dec. 29, is published with our present issue. A copy will be sent gratis to subscribers on receipt of a postcard addressed to the Manager of THE LANCET, 7, Adam Street, Adelphi, W.C.2. Subscribers who have not already indicated their desire to receive indexes regularly as published should do so now.

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35220

Public Health

SPREAD OF ADULT-TYPE PULMONARY TUBERCULOSIS IN CONTACT HOUSEHOLDS

JOHN ASPIN
M.A., M.D. Camb., D.M.R.D.
CHEST PHYSICIAN, LEEDS

COMPARED with the general population, households containing tuberculosis contacts have a higher tuberculosis attack-rate; and, without overlooking possible effects of heredity and environment, it is generally assumed that the excess morbidity is causally connected with the extra risk of infection at home.

For these reasons it is usual to attempt to examine all the original household contacts of newly notified cases. Many chest clinics also try to arrange for the periodic review of certain groups of originally healthy contacts, in the hope of picking out for treatment persons on the point of falling ill. Which groups can most productively be kept under observation? For how long should each be seen? How much annually recurring work will their examination entail? And how much tuberculosis will the programme disclose, compared with other methods of case-finding?

THE LITERATURE

The relevant information published in this country does not enable us to answer these questions, and lack of data may partly explain why the opinions expressed in the selected bibliography (see below) differ so widely. During the past two decades the emphasis has been shifting from the clinical examination of children to the regular radiological review of adolescent and young adult contacts. In these days of financial stringency and overcrowded clinics it would be comforting to the clinician to know more about the likely value of the various procedures, measured in terms of cases found. Such information I have tried to supply here. By careful planning, and by restricting the scope of my investigation to the occurrence of real tuberculosis in real contacts of real cases, as defined below, it has been possible, without elaborate statistical analysis, to demonstrate clear-cut differences.

SELECTION OF INDEX CASES AND DEFINITION OF TERMS

According to the terminology of Frost (1936) an index case is the first reported case of the disease in question which draws attention to a household during the period in question.

Between Jan. 1, 1938, and Aug. 31, 1939, the chief clinical tuberculosis officer for the City of Leeds confirmed the notification of 889 new cases of pulmonary tuberculosis. 680 of these have been accepted by t as "index cases of adult-type pulmonary tuberculo in true Leeds residents notified during the period i question" or, in short, as "index cases." The 8 cases are listed in table I, which shows self-explanator subgroups of 209 rejected cases.

Cases occurring in the families of the 680 index cas are referred to throughout in the following way:

(1) Cases notified as adult-type pulmonary tuberculos are called "cases of pulmonary tuberculosis."

(2) "Previous" cases are previously notified cases o pulmonary tuberculosis in persons known to have lived i the households of index cases at relevant times up to twent five years before. Previous cases are said to have h "acceptable contact" with their index cases.

(3) "Subsequent" cases are original household contac who have been notified as cases of pulmonary tuberculo during the ten years following notification of the index case Subsequent cases are said to be "original contacts."

(4) Other "associated" cases of pulmonary tuberculos may be related to the index cases but lack acceptable contac For example, cases in persons who have lived out of tow for more than ten years, but have been occasional visitors can properly be called *associated cases.*

TABLE I—CASES OF PULMONARY TUBERCULOSIS NOTIFIED I LEEDS BETWEEN JANUARY, 1938, AND THE END OF AUGUST, 1939

Type of case	No. of cases
All cases of pulmonary tuberculosis notified between January, 1938, and the end of August, 1939	889
Primary pulmonary tuberculosis in persons aged less than 15	79
[illegible] coming to live in Leeds	47
[illegible] of institutions (students, mental defectives, and [illegible] and casual visitors to Leeds	35
Full records not preserved at the clinic	35
Otherwise acceptable cases notified in households where one case had already been notified during the period ..	13
	209
Acceptable index cases of adult-type pulmonary tuberculosis	680

By using these definitions the study can be confined to adult-type pulmonary tuberculosis recorded in persons who were or had been household contacts of th index cases. For the sake of completeness, occasiona reference will be made to "associated" cases of pul monary tuberculosis, but cases of this type are no included in the main calculations.

MORTALITY AND INFECTIVITY IN INDEX CASES

Before dealing with the previous and subsequent experience of pulmonary tuberculosis in the familie it is desirable to give some brief details about the inde cases themselves. It will suffice to set out the di tribution by age and sex and the mortality among th

TABLE II—DISTRIBUTION OF INDEX CASES BY AGE AND SEX

(In this and subsequent tables "positive" means "ever positive to smear," and "negative" means "negative to smear" or "not tested")

—	Age (yr.)							Total
	10–14	15–19	20–24	25–34	35–44	45–64	65 +	
Males:								
Positive ..	—	20 (*6·5%*)	34 (*11·0%*)	55 (*17·9%*)	69 (*22·4%*)	115 (*37·3%*)	15 (*4·9%*)	308
Negative ..	3 (*2·8%*)	13 (*12·3%*)	8 (*7·5%*)	21 (*19·8%*)	16 (*15·1%*)	43 (*40·6%*)	2 (*1·9%*) ..	106
Total ..	3 (*0·7%*)	33 (*8·0%*)	42 (*10·1%*)	76 (*18·4%*)	85 (*20·5%*)	158 (*38·2%*)	17 (*4·1%*)	414
Females:								
Positive ..	2 (*1·0%*)	41 (*21·0%*)	45 (*23·1%*)	52 (*26·7%*)	38 (*19·5%*)	14 (*7·2%*)	3 (*1·5%*)	195
Negative ..	2 (*2·8%*)	12 (*16·9%*)	10 (*14·1%*)	22 (*31·0%*)	15 (*21·1%*)	10 (*14·1%*)	—	71
Total ..	4 (*1·5%*)	53 (*19·9%*)	55 (*20·7%*)	74 (*27·9%*)	53 (*19·9%*)	24 (*9·0%*)	3 (*1·1%*)	266
Grand total ..	7 (*1·0%*)	86 (*12·7%*)	97 (*14·3%*)	150 (*22·0%*)	138 (*20·3%*)	182 (*26·8%*)	20 (*2·9%*)	680

TABLE III—SURVIVAL OF INDEX CASES

			Years after notification										Total 10 yr. after notification
			0–1	1–2	2–3	3–4	4–5	5–6	6–7	7–8	8–9	9–10	
ositive	Males 308	Dead	130	40	31	17	11	5	8	7	6	2	257
		Lost sight of	..	5	2	..	1	..	..	..	..	..	8
	Females 195	Dead	70	23	17	8	7	7	3	5	4	..	144
		Lost sight of	2	6	3	1	..	..	..	..	2	..	14
	Total 503	Dead	200	63	48	25	18	12	11	12	10	2	401
		Lost sight of	2	11	5	1	1	..	..	..	2	..	22
egative	Males 106	Dead	29	4	4	4	2	1	..	1	2	1	48
		Lost sight of	2	3	..	1	1	1	1	..	1	..	10
	Females 71	Dead	14	3	2	1	..	..	1	..	..	..	21
		Lost sight of	4	4	2	1	4	..	..	1	1	1	18
	Total 177	Dead	43	7	6	5	2	1	1	1	2	1	69
		Lost sight of	6	7	2	2	5	1	1	1	2	1	28
Grand total 680		Dead	243	70	54	30	20	13	12	13	12	3	470
		Lost sight of	8	18	7	3	6	1	1	1	4	1	50
ercentage surviving to end of period			63·8	53·0	44·4	39·6	36·3	34·2	32·2	30·0	28·0	27·5	...

ases (tables II and III and figs. 1–3). The crude figures ccord with the general findings throughout the country, nd support the view that the families of the index ases provide a suitable population for statistical study.

In calculating survival factors, cases marked off as ecovered in more than 5 but less than 10 years after otification are presumed still to be living. The group "lost sight of" includes cases transferred to other areas and not followed up: these cases have been excluded after the last interval through which they have been traced. As is customary, the survival factors for the separate intervals have been multiplied together to produce overall factors (table III).

The mortality figures have not been adjusted to allow for expected deaths other than from tuberculosis. In the present context death or survival of potentially infectious persons is of more interest than death strictly referable to tuberculosis.

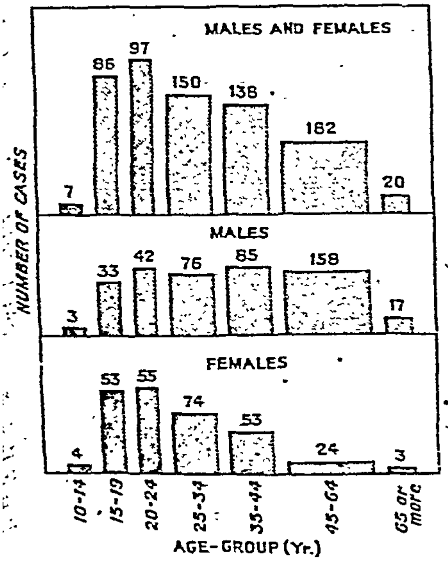

Fig. 1—Distribution of index cases of adult-type pulmonary tuberculosis by age and sex.

DISTRIBUTION OF PREVIOUS AND SUBSEQUENT CASES

How many previous and subsequent cases of pulmonary tuberculosis have been recorded in the families of the 680 index cases?

At the clinic there is an elaborate system of cross-entry of notifications on the case-papers of relatives, whether alive or dead, and entries of this type, together with a study of the case-histories of the index cases, have readily disclosed the names of the "previous" cases. Examination of individual records has settled outstanding questions about the diagnosis or the degree of household contact.

Similar cross-entries have revealed practically all the names in known subsequent cases, although here a further check has been possible, in that the case-papers of all original contacts seen at the clinic are available for examination. Although the proportion of original contacts examined at the clinic varied from 62% in youngsters aged less than fifteen to 42% in those between fifteen and thirty-five, it is believed that a far greater proportion of the subsequent cases have been notified; for, although healthy adolescent contacts are often hard to handle, those with progressive symptoms come very readily to diagnosis when there has been another case in the family.

The distribution of previous and subsequent cases in the 680 families of index cases is shown in fig. 4.

The most striking thing about this distribution is that 498 (73%) of the families contain no previous or subsequent case of pulmonary tuberculosis as defined above. No system of contact review could have revealed the index cases developing in these families. They had been infected by persons undiscovered at times unknown. Their disease became manifest through the interaction of unpredictable factors. They came to diagnosis in the course of the investigation of patients referred for an opinion.

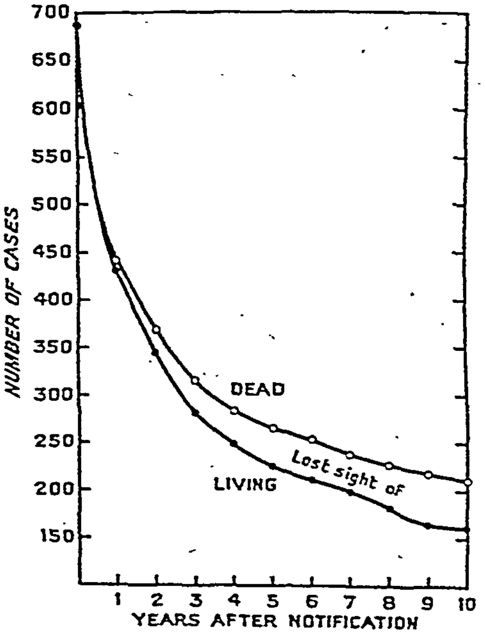

Fig. 2—Survival in 680 index cases of pulmonary tuberculosis.

In 135 families (20%) there were previous cases, in 70 (10%) there were subsequent cases. 23 (3%) of the families contained both previous and subsequent cases, a narrow but important overlap to which further reference will be made.

Since subsequent cases of pulmonary tuberculosis were eventually notified in 70 (10%) of the families there was a clear need for contact examination.

TIME-SPREAD OF PREVIOUS AND SUBSEQUENT CASES

There are many ways of tabulating these things. The method selected will be of interest to the clinician who has to decide for how long each contact should be kept under review.

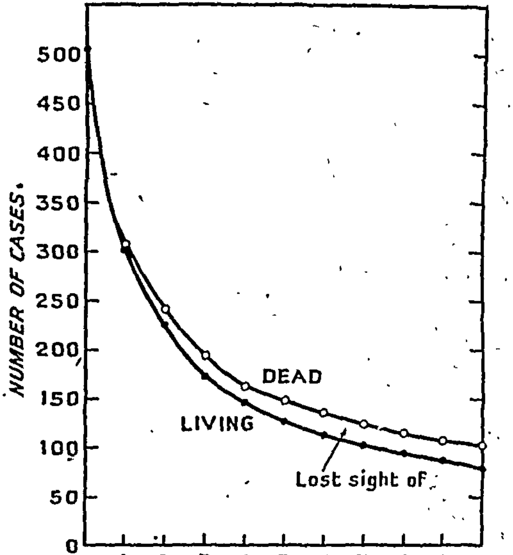

Fig. 3a—Survival in 503 index cases ever proved "positive."

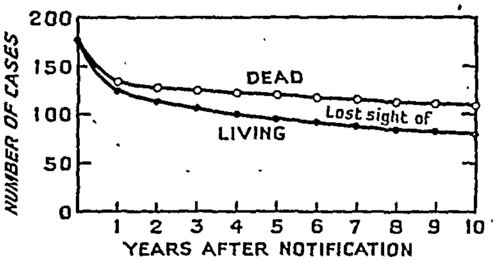

Fig. 3b—Survival in 177 index cases never proved "positive."

In fig. 5 (based on table IV) the central vertical line shows the instant of notification of the 680 index cases. In each case with a tuberculous family history we know how long it was since the family contained another person suffering from tuberculosis; and these intervals since the last known family contact are represented to the left of the central vertical line. The height of the columns indicates the number of cases in which the interval was one year, two years, &c. To give an example, if an index case was notified in 1938, and the last previous patient in that family died in 1935, the entry on the left-hand side of the figure would be in the "not alive after the 4th year before" column.

To the right of the central line are represented the intervals between notification of the index cases and notification of a subsequent case in that patient's family. The heavily shaded part of the columns shows the year of notification of these subsequent cases in families where a case had been notified before the index case.

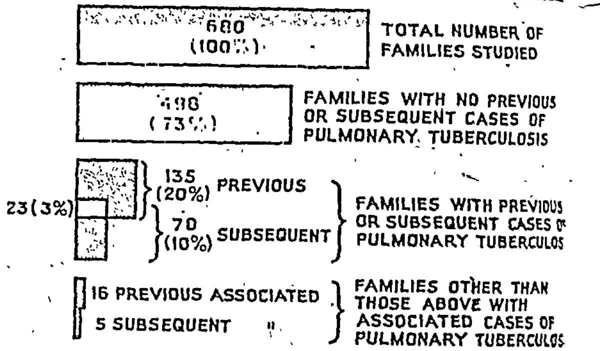
680
(100%)
TOTAL NUMBER OF FAMILIES STUDIED
498
(73%)
FAMILIES WITH NO PREVIOUS OR SUBSEQUENT CASES OF PULMONARY TUBERCULOSIS
23 (3%)
135
(20%)
PREVIOUS
70
(10%)
SUBSEQUENT
FAMILIES WITH PREVIOUS OR SUBSEQUENT CASES OF PULMONARY TUBERCULOS
16 PREVIOUS ASSOCIATED
5 SUBSEQUENT "
FAMILIES OTHER THAN THOSE ABOVE WITH ASSOCIATED CASES OF PULMONARY TUBERCULOS

Fig. 4—Families with other cases of pulmonary tuberculosis notifie previously or subsequently to the index cases.

Although there is a wide spread, it is noteworthy th there was a previous case alive within a year of th notification of the index case in 51 families (38% o all index families with previous cases), and that a subsequent case was notified during the next year in 3 families (49% of all index families with subsequen cases). The number of further cases notified was fa and away greater in the first year than in any other year; and, by the time five years or more had elapsed after contact was first recognised or last recorded further cases were much less frequent.

There is another point. Although there were onl 23 families with both previous and subsequent case in addition to the index case, these complex familie contained 19 out of the 36 subsequent cases notifie after the first year.

HANDLING OF FAMILIES WITH SPUTUM-NEGATIVE INDEX CASES

What was the relative proportion of subsequent case in families with sputum-negative index cases? 12 (6·8% of the 177 families in this group contained subsequen cases within ten years, as compared with 58 (11·5% of the 503 families with sputum-positive index cases.

However, 5 of the 12 "negative" families as define had recently contained some sputum-positive case o pulmonary tuberculosis other than the index, who migh have infected the subsequent cases.

The figures therefore suggest that *families in which th only case is sputum-negative are materially less likely t contain subsequent cases*; but that, until the recen

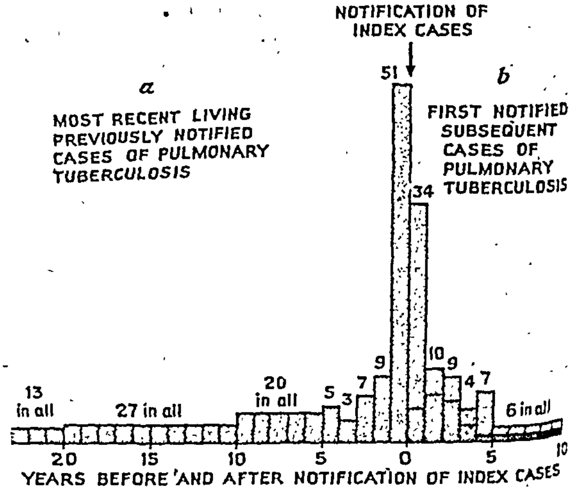

Fig. 5—Distribution of (*a*) most recent living previously notified cas of pulmonary tuberculosis and (*b*) first-notified subsequent cases o pulmonary tuberculosis, in persons in acceptable household conta with the index cases. Shaded areas in *b* represent families wi both previous and subsequent cases.

or present existence of further sputum-positive cases has been disproved, the families of sputum-negative cases should be examined just as thoroughly as the others—a rather obvious conclusion.

SUBSEQUENT CASES

Table V shows the comparative age-distribution of the 457,411 inhabitants of the City of Leeds in 1939, the 680 index cases of pulmonary tuberculosis, and the 1934 original household contacts. The table shows that over half of the index cases were between fifteen and forty-five years old and that inevitably there is a relative excess of contacts aged less than twenty-five. 85 subsequent cases were notified in the 70 families in which there were cases of this type.

TABLE IV—DISTRIBUTION OF MOST RECENT LIVING PREVIOUSLY NOTIFIED CASES OF PULMONARY TUBERCULOSIS AND FIRST NOTIFIED SUBSEQUENT CASES OF PULMONARY TUBERCULOSIS DURING YEARS BEFORE AND AFTER NOTIFICATION OF INDEX CASES

Years *before* notification of index cases	Most recent living previous cases of pulmonary tuberculosis	
	All families	23 families with subsequent (and also previous) cases
20 +	13	1
10–20	27	5
5–10	20	4
4–5	5 } 24	1 } 9
3–4	3	1
2–3	7	3
1–2	9	4
0–1	51	4
Total	135	23

Years *after* notification of index cases	First notified subsequent cases of pulmonary tuberculosis	
	All families	23 families with *previous* (and also subsequent) cases
0–1	34	4
1–2	10 } 30	6 } 14
2–3	9	5
3–4	4	2
4–5	7	1
5–10	6	5
Total ..	70	23

Table VI shows the age-distribution of the subsequent cases at the time of notification of their index cases and at the time of their own notification. Only 2 out of 558 contacts aged less than fifteen at the time of notification of their index case were eventually notified before reaching the age of fifteen, whereas 7 from this age-group and another 76 from the 1376 contacts aged more than fifteen at the time of notification of their index case were subsequently notified. The conclusion is that, if Mantoux-positive children aged much above the age of five have not got tuberculosis when contact is first recognised, few cases will be missed if regular review of these contacts is deferred until they reach the age of fifteen.

TABLE V—AGE-DISTRIBUTION OF POPULATION OF CITY OF LEEDS, 1939; INDEX CASES OF PULMONARY TUBERCULOSIS; AND ORIGINAL HOUSEHOLD CONTACTS OF INDEX CASES

Age-group (yr.)	Leeds population in 1939	Index cases of pulmonary tuberculosis	•Household contacts of index cases
0–4	29,194 (*6%*)	—	163 (*8%*)
5–9	48,275 (*11%*)	—	193 (*10%*)
10–14		7 (*1%*)	202 (*10%*)
15–19	39,131 (*9%*)	86 (*13%*)	224 (*12%*)
20–24	31,406 (*7%*)	97 (*14%*)	186 (*10%*)
25–34	79,573 (*17%*)	150 (*22%*)	254 (*13%*)
35–44	74,815 (*16%*)	138 (*20%*)	275 (*14%*)
45 or more	154,687 (*34%*)	202 (*30%*)	437 (*23%*)
Total ..	457,411	680	1934

TABLE VI—AGE-DISTRIBUTION OF SUBSEQUENT CASES OF PULMONARY TUBERCULOSIS AT TIME OF NOTIFICATION OF THEIR INDEX CASES AND AT TIME OF THEIR OWN NOTIFICATION

Age-group (yr.)	Subsequent cases	
	At notification of index cases	At own notification
0–9	1 (*1%*)	0
10–14	8 (*10%*)	2 (*2%*)
15–24	31 (*36%*)	33 (*39%*)
25–44	34 (*40%*)	35 (*41%*)
45 +	11 (*13%*)	15 (*18%*)

By calculations based upon tables III and VII, the survival of the index cases and of the subsequent cases can be compared. Table VIII sets out the results of these comparisons, together with figures for the infectivity of the two groups. One's first thought is that it is disappointing to find that the subsequent cases, which might be assumed to have benefited from earlier investigations and diagnosis, do not show a materially better prognosis. However, on reflection it must be realised that the subsequent cases include a proportion of gross unrecognised cases brought to light after the diagnosis of a secondary index case, and also a proportion of secondary cases who have refused to attend the clinic until advancing disease has rendered them unfit for work.

RELATIVE ATTACK-RATE IN CONTACT POPULATION

Far and away the most tempting thing to do with the statistics so far presented is to attempt to compare the observed incidence of subsequent cases in contact households with the expected attack-rate for a similarly sized sample of the population of the City of Leeds. It is fully realised that such comparisons can only justifiably be made by those who have kept a suitably selected sample of the population under observation for the whole of the period in question, ten years in this case. The present investigations, going backwards as they do instead of forwards in time, fall short of these requirements. But since there seems to be no record of a statistically satisfactory British investigation of this type, I put forward the following comparisons:

(1) The notification of 680 index cases of adult-type pulmonary tuberculosis in the City of Leeds represents an annual attack-rate of 0·89 per thousand of the whole population.

TABLE VII—SURVIVAL OF 85 SUBSEQUENT CASES

Years after notification	0–1	1–2	2–3	3–4	4–5	5–6	6–7	7–10	Known to be alive after 10 yr.
Died ..	15	10	10	4	3	5	4	3	} 28
Lost sight of	—	2	1	—	—	—	—	—	

(2) By calculating age-specific rates from table V it is possible to work out the attack-rate for a sample of 1934 from the general population which is of the same age-distribution as the contacts but random in other similar respects. This sample might be expected to produce rather less than 2 cases of pulmonary tuberculosis per year during the next ten years: 1·61 in the first year, rising gradually to 1·79 in the tenth year, with a total expectation of 17·12 (see table IX).

(3) In fact 85 cases have been notified during the ten years among the 1934 original household contacts of newly notified index cases, five times as many as would be expected. The difference is surely attributable to the effects of living in tuberculous households.

(4) The excess morbidity is unevenly spread over the years following "notification" of the index cases. Again, assuming an expected development of cases as in table IX, comparison

TABLE VIII—COMPARISON BETWEEN INDEX AND SUBSEQUENT CASES OF PULMONARY TUBERCULOSIS

—	Index cases	Subsequent cases
All cases	680	85
Positive cases	503 (74%)	54 (64%)
Negative cases	177 (26%)	31 (36%)
% surviving for 2 years ..	53·0	70·2
% surviving for 10 years ..	27·5	34·6

with the observed figures shows the development of: (*a*) 22 times as many subsequent cases in the 1st year; (*b*) 8 times as many in years 2 and 3; (*c*) 4 times as many in years 4 and 5; and (*d*) no excess in the subsequent years up to 10.

It is therefore clear that the original review of all household contacts to newly notified cases is absolutely *essential, that for five years after exposure to a newly* notified case regular review should disclose many times as many cases as would be found in the general population, and that, after five years, review of these contacts may reveal no more disease than does examination of the general population.

DISCUSSION

In dealing with tuberculous households the next most important thing after arranging for the treatment of the newly diagnosed index case is to make sure that all original contacts are seen at once. If they are aged less than fifteen they should be examined and tuberculin-tested. If they are tuberculin-positive or above fifteen they should be seen and radiographed. In the American phrase, all this is a "MUST," the only permissible relaxation being that those who refuse to attend for clinical examination should be persuaded to attend for radiography alone. It goes without saying that the tuberculin-negative contacts will be offered B.C.G. vaccination, that the contacts with primary or non-pulmonary tuberculosis will be given suitable advice, and that the suspected or manifest cases of adult-type disease will be appropriately handled. When all this has been done, the back of the contact problem will have been broken.

TABLE IX—COMPARISON BETWEEN EXPECTED AND ACTUAL DEVELOPMENT OF PULMONARY TUBERCULOSIS AMONG CONTACT POPULATION (PREVAILING AGE-SPECIFIC RATES FOR CITY OF LEEDS HAVE BEEN USED IN CALCULATING EXPECTED DEVELOPMENT OF DISEASE)

Index cases	Cases of pulmonary tuberculosis in contact population		
Year after notification	Expected	Actual	Actual/expected ratio
1	1·61	36	22·4
2 and 3	3·30	25	7·6
4 and 5	3·40	14	4·1
6–10	8·81	10	1·1
Up to 10 years ..	17·12	85	5·0

Which groups of *originally healthy contacts should be* kept under review, and for how long should each be seen? My figures suggest that the attack-rate among contacts, high at first, has declined almost to that *expected in the general population within five years* of the last known effective domiciliary exposure either to a new case or to surviving still infectious old ones. After annual radiography for this period, perhaps at the local mass-radiography unit, the missionary zeal of the health visitors and office staff who have been trying to *secure regular attendance can be employed* more productively in dealing with the unwilling among the contacts of the next generation of index cases. In general, this principle is applicable to contacts between the ages of fifteen and thirty or thirty-five.

Contacts over thirty-five whose radiographs are clear a year after the last effective exposure could probably be dismissed from observation. The work of S[illegible] (1951) *suggests that the subsequent development* o pulmonary tuberculosis is rare in females who had clear radiograph at the age of thirty-five, and it i suspected that the bulk of the cases developing in middle-aged and older men are the recrudescence of earlie arrested and often unsuspected lesions.

At the other extreme of life I agree in principle with Tattersall (1951), who would "put off till puberty" the review of tuberculin-positive children who have remained well for a few months *after their first examination*. Figures given in table VI support this policy. It is still far from clear whether or not children in this *category suffer a raised attack-rate in* adult life compared with other *tuberculin-positive children, and until these* things have been decided it will be as well to review the cases at puberty and perhaps to offer them a periodical X-ray *examination at the* mass-radiography unit.

Finally it is emphasised that the full programme set out above is only applicable to "real" contacts of "*real*" *cases. The programme will undergo continued* modification by the clinician who is aware of the medical and social background of the families. When further cases develop, or in families with multiple cases living under adverse and irremediable conditions, even more frequent review *may* occasionally be required; but where contact has been casual, or has occurred *only* after the successful treatment of the only case, contacts can probably be dismissed from observation after one examination or, *at the* most, two. Time *saved in this way can be used more productively in dealing* with the "real" contacts, who are at extra risk.

SUMMARY

Clinic records relating to the families of 680 index cases of pulmonary tuberculosis have been studied for more than ten years before and ten years after the notification of these cases, in an attempt to provide a factual basis for contact-review programmes.

In 498 families (73%) there were neither "previous" nor "subsequent" cases of pulmonary *tuberculosis* as defined in the text. In 135 families (20%) there were "previous" cases, in 70 (10%) there were "subsequent" cases, and in 23 (3%) there were both.

A table has been prepared to show *the occurrence in* time, compared with the date of *notification* of the index cases, of the last *surviving* "*previous*" cases still suffering from pulmonary tuberculosis and the first notified "subsequent" cases in the relevant families. Table IV shows *that* the number of "subsequent" cases notified was *far and away greater* in the first year than in any other year, and that by the time five years had elapsed "subsequent" cases were *much less frequent*.

In other sections, *figures* are set out to *show* the *age*, infectivity, and *survival* of the index-cases and the "subsequent" cases, and the age-groupings among the general population of Leeds at that time.

Comparison has then been made between the observed and expected morbidity *from* adult-type pulmonary tuberculosis among the contact population of 1934. Whereas 17 "subsequent" cases might have been expected to develop during the ten-year period, in fact 85 were *notified, five times as many. Moreover*, the excess was unevenly spread out over the years following notification of the index cases, there being 22 times the expected number of "subsequent" cases in the first year, 8 times as many in years 2 and 3, and 4 times as many in years 4 and 5. However, there was no excess in subsequent years up to 10.

The implications of these findings as applied *to programmes for the review* of contacts are discussed. The figures presented make it possible to estimate the work nvolved in carrying out any selected programme of his type, and the likely yield of subsequent cases.

In a sense, this account is a tribute to all the clinic's health isitors and office staff who have secured the attendance f unwilling contacts during the past decades, and to Mr. F. H. Vood, the administrative officer in charge of records throughut the period. I wish to thank the research committee f the British Tuberculosis Association for advice, encouragenent, and a grant to cover expenses, and Mr. B. Benjamin, B.SC., F.I.A., statistician to the public-health department of the London County Council, for invaluable help in the presentation and statistical interpretation of the records.

SELECTED BIBLIOGRAPHY

Chadwick, H. D., Pope, A. S. (1942) The Modern Attack on Tuberculosis. London.

Cox, G. L., et al. (1929) *Tubercle*, 10, 497.

Deeny, J. (1947) *J. med. Ass. Eire*, 21, 82.

Dow, D. J., Lloyd, W. E. (1931) *Brit. med. J.* ii, 183.

Frost, W. H. (1936) Memorandum on Studies of Tuberculosis. Williamson County, Tennessee.

Israel, H. L., DeLien, H. (1942) *Amer. J. publ. Hlth*, 32, 1146.

Opie, L., McPhedran, F. M. (1926) *Amer. Rev. Tuberc.* 14, 347.

— —, Putnam, P. (1935) *Amer. J. Hyg.* 22, 644.

Puffer, R. R. (1950) Practical Statistics in Health and Medical Work. New York.

— Doull, J. A., Gass, R. S., Murphy, W. J., Williams, W. C., (1942) *Amer. J. publ. Hlth*, 32, 601.

Springett, V. H. (1951) *Brit. med. J.* ii, 144.

Stewart, H. C., Gass, R. S., Gauld, R. L., Puffer, R. R. (1937) *Amer. J. Hyg.* 26, 527.

Tattersall, W. (1951) *Tubercle*, 32, 16.

Wood, W. B. (1929) *Tubercle*, 11, 8.

— (1930) *Ibid*, 11, 489.

Variola Minor in Lancashire

The total number of cases of variola minor ascertained up to the morning of last Tuesday, March 4, was 70—64 in Rochdale, 5 in Milnrow, and 1 in Heywood. All these cases are associated with the original focus in Rochdale. 37 patients are in hospital; the remainder are no longer infectious. Up to March 3 the cases had arisen in the direct line of contact. On March 3, 4 were found which could not be associated with previous cases.

Infectious Diseases in England and Wales

Disease	Week ended Feb.			
	2	9	16	23*
Diphtheria	24	34	48	37
Dysentery	490	592	636	591
Encephalitis:				
Infective	4	2	1	3
Postinfectious	1	1	2	2
Food-poisoning	94	89	114	85
Measles, excluding rubella	3386	4430	4980	5734
Meningococcal infection	31	49	51	45
Ophthalmia neonatorum	30	35	27	40
Paratyphoid fever	6	6	3	6
Pneumonia, primary or influenzal	1005	1105	1175	1143
Poliomyelitis:				
Paralytic	17	11	13	9
Non-paralytic	8	6	7	5
Puerperal pyrexia and fever	257	216	226	218
Scarlet fever	1320	1416	1482	1613
Smallpox	..	..	1	18
Typhoid fever	5	2	3	3
Whooping cough	2655	2686	2550	2648

* Not including late returns.

Special Articles

GENERAL MEDICAL COUNCIL

FEB. 26

An extra session of the General Medical Council was held on Feb. 26: and this was followed in the afternoon by a meeting of the Medical Disciplinary Committee.

DISCIPLINARY BUSINESS

The council did not direct the Registrar to erase from the Register the names of *Roger St. Aubyn*, registered as of 18, Redcliffe Square, London, S.W.10, M.R.C.S. (1946), and *Frederic Syson*, registered as of 52, Station Road, Horsforth, Leeds, M.B. Glasg. (1925). Judgment in these cases of misdemeanour had been postponed, and the two doctors appeared and presented testimonials.

VACANCY ON MEDICAL DISCIPLINARY COMMITTEE

Major W. J. Anstruther-Gray, M.P., was appointed a member of the Medical Disciplinary Committee, in the place of another lay member, Miss Florence Horsbrugh, who resigned from the council on being appointed Minister of Education.

PROVISIONAL AND FULL REGISTRATION

The council considered the report of a special committee on provisional and full registration. The President, who was chairman of the committee, said that legislation giving effect to arrangements made previously between the United Kingdom Government and the government of the Irish Republic had now been passed in Ireland, and the Irish authorities were prepared to adopt Jan. 1, 1953, as the operative date for introducing arrangements for compulsory intern service.

The Commonwealth Relations Office had suggested that the council should furnish a memorandum describing the way in which applications for registration by virtue of Commonwealth diplomas would be dealt with after the appointed day. The committee had drawn up such a memorandum, in which they indicated that they felt it was not practicable for the council to specify at this stage any general criteria by which applications for registration based on experience (other than service for 12 months as house-officer in suitable hospitals) would in due course be determined. They recommended—and the council agreed—that to deal with applications a small committee should be appointed. This would be appointed at the November session, and would consist of a physician, a surgeon, a member engaged in general practice, and the president ex officio.

The applicants would appear to fall into three categories: (1) those with not less than 12 months as house-officers under compulsory internship schemes, substantially equivalent to the scheme in this country, which had been brought into operation in the territories where their diplomas were obtained; (2) those who had gained 12 months' experience as house-officers but not under compulsory internship schemes; and (3) others.

With regard to (1), at present the Union of South Africa and New South Wales insisted on internship; New Zealand proposed to bring a scheme into operation, but the date was not yet fixed. There was no doubt that other Commonwealth countries would do the same as time went on. There would be no difficulty with applicants in this category. The special committee would consider if the schemes were substantially the same as in the United Kingdom; and if they were registration would be automatic. Categories (2) and (3) would be considered sympathetically on their merits in each individual case.

COMPULSORY HOUSE-APPOINTMENTS

The committee on provisional and full registration also considered the nature and form of the evidence as to selection for employment which applicants for provisional registration should be required to submit under the Medical Act, 1950. The committee felt that it was highly desirable on administrative grounds that the evidence to be produced for the purpose of satisfying the appropriate registrar that an applicant had been selected for employment as a house-officer, should be simple and uniform and should give no occasion for doubt or for further inquiries on behalf of the council. They therefore suggested a short form of certificate. The council approved this. It also agreed that a further form of certificate should be brought to the notice of licensing bodies and medical schools. The committee's report explained that the first certificate contained no reference to the nature of the post, duration of employment, or date on which the applicant was to take up duty, these particulars not being the concern of the registrar. It was understood, however, that licensing bodies and schools would desire to receive such information, and the committee believed that it would be convenient if a certificate in common form were devised.

Sir Henry Wade said that everyone was enthusiastic about the compulsory house-appointment scheme. They also knew that the time of graduation varied, and there might be a gap of some months between graduation and the hospital appointment. Was the young graduate to be given any opportunity to do something useful in medicine in this period ?

Dr. J. G. McCrie raised the question of whether the posts would be filled by applicants in the provisional registration category. He understood that the Ministry of Health were considering confining appointments to such persons. The posts might be available, but who was to compel hospital management committees to appoint a provisionally registered person ?

The President remarked that he thought a question might be put in the House of Commons.

Medical Disciplinary Committee

The President was in the chair at the meeting of the Medical Disciplinary Committee.

APPEALS

It was reported that *Arthur James Daly*, whose name the committee had directed in November, 1951, to be erased from the Register, had lodged a petition of appeal. It was also stated that on Jan. 30, 1952, His Majesty approved an Order in Council granting leave to *Jack Michael Sinclair* to withdraw the appeal brought by him against the determination of the committee in July, 1951, that his name should be erased from the Register. The erasure thereupon took effect on Jan. 30, 1952.

APPEAL FOR FREE PARDON

Mr. Stuart Horner, counsel, applied for an adjournment in the case of *Sumatapalage Reginald Gunewardene*, registered as of 53, East Dulwich Road, London, S.E.22, L.M.S.S.A. (1942), who had been summoned to appear on a charge of having been convicted at the Central Criminal Court in March, 1951, of unlawfully killing Grace MacLean, for which he was ordered to be imprisoned for three years. Mr. Horner stated that an application for Her Majesty's free pardon had been drawn up, but there had been some difficulty in getting it signed at Maidstone Jail. The application for adjournment was granted.

ADJOURNED CASE

The Committee considered the case of *Harold Stanley Groves*, registered as of The Poplars, Blagreaves Lane, Littleover, Derby, M.R.C.S. (1915). In May, 1951, the committee found him to have been convicted in 1949 of driving a motor-car while under the influence of drugs, and in 1951 of being under the influence of drink so as to be incapable of having proper control of a motor-car. Dr. Groves was then represented by a solicitor but did not appear. The President, announcing that judgment would be postponed until the sitting in November, 1951, said that the committee would wish to see Dr. Groves. In the November session the committee, having regard to the illness of the practitioner, postponed judgment until the present sitting.

Dr. Groves was not present, but his wife attended. The President said that the rules provided that a practitioner could be represented by a member of his family. The committee postponed judgment until their session in May.

ALLEGED ABORTION

Charles Locksley Bikitsha, registered as of Butterworth, C.P., South Africa, M.B. Edin. (1941), was charged with having been convicted at Birmingham Assizes on July 9, 1951, of unlawfully using in April, 1951, an instrument or other unknown means and administering a poison or other noxious thing to procure the miscarriage of a woman named Margaret Malone, and of administering a poison or other noxious thing to Joan Ali with intent to procure a miscarriage, for which he had been sentenced to two months' imprisonment.

Mr. A. P. Marshall, Q.C., for Dr. Bikitsha, applied for t hearing to be in camera. He said that Dr. Bikitsha was apparent to a paramount chieftainship in South Africa, there might be repercussions beyond the circumstances the case if it were taken in public. In answer to the Presiden Mr. Marshall said that the trial was not in camera; th was no power to hear it in camera at the assize, but th Committee had the power and discretion, and he asked them to use this in Dr. Bikitsha's favour. The committee decid to hear the case in public.

After hearing evidence the committee directed the Registra to erase from the Register the name of *Charles Locksle Bikitsha*. This is subject to notice of appeal.

STEROID HORMONES AND BEHAVIOUR

Speaking at Edinburgh University on Feb. 25, Prof. Marc Klein appealed for closer harmony betwee clinicians and workers in the fundamental sciences. He described his team in Strasbourg as comprising a surgeon, a psychologist, a biochemist, and a biologist.

Without accepting the philosophical implications of the idea of behaviourism originated by J. B. Watson, Professor Klein defined behaviour as the observable and overt activities of animals under controlled conditions. Specific behaviour patterns can be seen in rodents and other animals over periods of months and years, particularly with reference to nesting, feeding, and sexual activities. Once such patterns have been consistently observed in the laboratory, factors which modify them may be studied. He described experiments, begun twenty years ago, suggesting that the nesting behaviour of rats, which normally starts before the birth of the young, is not determined by the presence or size of the uterus as was once supposed. Similar behaviour may be seen in animals from which the fœtuses and uterus have been removed; and in both the behaviour is apparently determined by hormonal changes, which are reflected in alterations in the rate of follicle maturation and in the disintegration of the corpus luteum.

More recently Professor Klein has carried out experiments designed to evaluate factors involved in sexual behaviour patterns in the rabbit. Spayed and hysterectomised females are known not to be receptive to males. If injected with œstradiol benzoate or testosterone, these animals accept the male repeatedly on any day, and continue to do so as long as injections are given. Similar results were obtained by implanting these hormones under the skin of the ear. From these observations it appears that such compounds are potent determinants of sexual behaviour, and that testosterone can initiate a typically female behaviour. However, when spayed female rabbits into which testosterone has been injected or implanted are brought in contact with normal female rabbits, the former exhibit a typically male attitude to the normal females. From this it may be concluded that environment has a dominant rôle in reversing the hormone effect.

Professor Klein recalled well-known endocrine disorders in man which are associated with psychological and behaviour abnormalities. These include Cushing's syndrome, precocious puberty, and the adrenogenital syndrome. Some of these conditions are cured by surgical removal of the causal tumour; after which behaviour reverts to normal. In other cases the abnormal behaviour pattern is fixed and is not altered by such therapy; in such cases environmental factors are apparently still operating and maintaining the abnormal social attitudes and habits.

Professor Klein drew no firm conclusions on the respective importance of hormonal and environmental determinants in behaviour, and advised caution in interpreting human behaviour on the basis of animal experiments; and he appealed for systematic study of individual cases of this type, with a view to elucidating the sources of human attitudes and habits.

In England Now

Running Commentary by Peripatetic Correspondents

It is high time that the U.R.S.L.S. took action, or at y rate protested sharply, against this habit, chronic d apparently increasing among lecturers, of spreading eir light in dark places. We are all painfully familiar th the situation. The distinguished physician or rgeon is introduced by the chairman in a few well-osen words. Though we know them by heart we plaud civilly. The lecturer rises, receives a great big nd, thanks the chairman, tells us what an honour it to be invited to address us, makes one joke, switches f the light, calls for the first slide, and talks for three-arters of an hour in Stygian tenebrosity. The luckless ribe whose duty it is to grasp and set down these arls so that they may be recorded for posterity in the edical press can only sit biting the end of his fountain-en in an agony of frustration, hoping that he will be le to remember with sufficient accuracy something of hat is being said. When all is over, the last question swered, and the vote of thanks passed, the scribe ntatively approaches the great man and asks if he ay borrow his notes, only to be informed that the cturer carries it all in his head. A summary is then ked for which, though glibly promised, seldom arrives. he U.R.S.L.S. ? Oh, the Union of Reporting Secretaries Learned Societies.

* * *

There are mornings in the late summer, still and early with a heavy dew on the lawn, which my gardener lways greets as "blighty weather." He, of course, is n ignorant dolt; whereas you and I know that the ilments his charges develop at those times are not due emanations or miasmata but to fungal and bacterial arasites. As members of the Faculty we know that revention is better than cure, so we slosh gallons of opper and/or sulphur compounds over the garden and e black spot in the roses or potato blight only two ears out of three. But now, it seems, we are as nearly ut of date as the gardener. As in human medicine, herapeutics in the garden is now all the go. My broad eans fail me, so far as I know, from two causes only: ice eat their seed or aphides suck their tips. But if hey should suffer—*absit omen*—from halo blight I can vercome this infection with *Ps. medicaginis* by applying treptomycin to their stems, or prevent it by soaking their eeds in a mixture of antibiotics before I plant them Mitchell, J. W., et al. *Science*, 1952, **115**, 114). Then, if brave the comments of my psychiatric colleague and row cacti, I can cure the beastly things of erwiniasis that's got you) by injecting them with penicillin (Boyle, . M. *Phytopathology*, 1949, **39**, 1029)—not that I would ift a syringe to save them.

There is said to be a great dearth of plant pathologists. o long as they are known by their bulging pockets and attered panamas I am sure the scarcity will continue. or the future a billycock, striped trousers, and a black ag must be de rigueur.

* * *

As the last chords of the symphony died away, tumul-uous clapping volleyed forth from the radio set. "Turn t off, for God's sake," growled our Scots surgeon. "I an't think why the B.B.C. don't cut out the applause. Horrible noise." "You like not?" asked the petite Austrian registrar, glancing up in surprise from her *Vogue*. "In Vienna we clap much. My mother, she haf one time burst her kid glove clapping Lotte Lehmann n *Der Rosenkavalier*!" "I'd like to meet your mother, Fraulein," boomed our orthopod. "I'm all in sympathy with her. When you hear good music you want to express your feelings in some way. Primitive people or children start dancing, but the best a concert audience can do is to clap vigorously." "H'mm," said Scotty, rather doubtfully, "but how is it that some people never clap?" "Too stuck up, or too repressed, perhaps. What do you think, Psyche?" "We—ell," our psychiatrist replied reflectively, "William James wrote something about never letting one's emotions be aroused at a concert without expressing them afterwards, even if it was by going home and speaking genially to one's grandmother." "Mark my words, Psyche," said our orthopod heavily, "the fellow who doesn't clap at a concert won't speak genially to his grandmother—if he expresses his emotions at all it's more likely to be by coshing the old lady on the head."

* * *

"These surgery chairs isn't so comfortable as they was, Mrs. Pinkle. Of course, it's not the doctor's fault—the epidemications, I mean. The country's goin' to pot, it is. Proper goin' to pot. As for the syringes, I've never seen like o' them, in twenty years of illness, with never a whole day's health, my dear. That's a fact. And then, just look at these 'ere new doctors. It's writ in their faces what they are. What are they? Well—this is 'Oly Week so I mustn't say unkind words habout anyone, must I? Look at this new Hamerican drug. Haureomycin, they calls it. Cures heverything—so they say. But they've still got cemeteries in Hamerica, haven't they? A streamlined send off, more likely.

"That's the new receptionist joost coom in. Bit giddy for my likin'. Don't fancy them kind mesself. Still, they moost have *some* sort of hability, if ye sees what I mean.

"There's Doctor complainin' habout 'is stethoscope again. Why don't Guvverment buy 'im a new one? Wouldn't cost 'em mooch and they've got tons of mooney. Oh, this coff of mine is gettin' worse. Carry me off yet, it will. I don't like the look in receptionist's eye, do you, luv?

"Wot kind o' medicine have you gettin'? It's doin' ye good? Mine isn't. Of course, my trooble is I know too mooch about mesself. Psycyclology. That's wot doctor calls it. Summat to do wi' yer brains, Mrs. Pinkle.

"And look at the size o' pills he's givin' us these days. Doctor's never been same since he got them new spectacles. Can't be right for his eyes. Well, dear, my turn next. Bye Bye. And—'ere—watch that young locomotive tendons. You know—doctor's deputy, of course. Clever chap. Harley Street some day. Or maybe—ha, ha—Dartmoor! Ye never can tell, luv. Look at Ruxton! Oh, me coff. It's gettin' worse. It's the agenised bread that's doin' it. Mark my words. Eee—GOOD mawnin', Doctor!"

* * *

"A certain quantity of zinc and zinc oxide may shortly be available from U.K. on allocation to the Federation for rubber processing and/or the pain industry."—H.M. Comptroller of Customs, *Singapore Standard*. I have occasionally prescribed zinc oxide, but I had not realised till then that I am employed in the "pain industry."

* * *

From the *Western Flying Post* (now the *Western Gazette*) for Jan. 9, 1826, I was pleased to learn that medical certificates were in vogue even then. We read how Jane Hawkins, silk weaver at Hillfarence, handed the Taunton bench the following certificate, "to which the name of an eminent surgeon at Wellington was subscribed," to show that illness had prevented her completing some work.

> Sirr I whill inform your oner that the said Jane Hawkins whas under my Care from the 24th of September unteel the 20th November 1825 and Whas not fit for th work Wieh shee Whas about Which Whas silk weaving and i tauld shee that shee Must not do it till the Disorder Do turn but shee told me that shee must try to Do out the Work so i niver ard from shee Afterwords—Which the said Jane Hawkins Do Ow Me that bill which his 10s Now for it. Dated 29 December, 1825.

The newspaper report remarks that "the damsel exhibited considerable surprise at the determined incredulity of the Magistrates as to the genuineness of the documents." Presumably they thought the writing too good to be true.

* * *

Overheard in a bus: "Of course he only does private practice—no health."

Letters to the Editor

CORNEAL GRAFTS

SIR,—The attention of Parliament has been called to consider an alteration in legislation so as to increase the supply of donor eyes by voluntary means for corneal graft surgery.

In recent years, thanks to the French revival and improvement of an old method which is mainly free from complications, the scope and safety of corneal grafting have been increased, and about 50% of suitable cases treated by this method show restoration of sight to varying degrees. The shortage of donor material is nationwide and becomes steadily greater since it mainly depends today on the use of pathological eyes which have to be removed for disease not affecting the cornea, while coincidentally the scope and applications of corneal graft surgery steadily expand.

Mr. B. W. Rycroft, who has been engaged in corneal graft surgery since 1936, has initiated a movement to obtain this alteration in the law and to ensure a legal and voluntary reservoir of adequate donor material. He should have the full support of our profession, and he has my entire encouragement also in his endeavours to place British ophthalmology in the forefront of international practice in corneal grafting. It is true that our eye surgeons have been badly hampered hitherto in this type of work by war, lack of special instruments, untrained personnel, and inadequate donor supplies. But only the shortage of donors now restricts the expansion of graft surgery in this country, and it is to be hoped that Parliament will wisely amend the old Anatomy Act to solve this difficulty, which obstructs modern eye surgery in the treatment of our fellow countrymen who are blind by corneal disease.

Royal College of Surgeons,
London, W.C.2.

CECIL WAKELEY
President.

PAIN IN THE BREAST

SIR,—I was very interested to read Mr. Mailer's letter (Feb. 23) about the aspiration of cysts in the breast, and there is no doubt that his view is shared by a number of responsible and experienced surgeons. Most surgeons who aspirate cysts are content only if clear fluid emerges and if, after aspiration, there is no suspicious nodularity remaining. It is true that the aspiration of the cyst requires no particular skill, but the selection of a suitable case and the interpretation of the results may well do so.

I did not have time in a lecture concerned with pain in the breast to deal adequately with this point, but my views about aspiration of cysts are expressed in *Surgical Progress*, 1951 :

> " Before elaborating this proposition (the surgical removal of a solitary lump), a word must be said about aspiration (of cysts). Aspiration is used for diagnosis and for therapy, and in neither instance is it satisfactory. As far as diagnosis is concerned, the needle may fail to find or penetrate the area in question, and no clear fluid be withdrawn where clear fluid exists, or conversely clear fluid may be withdrawn from a cyst adjacent to an early carcinoma. Further, although carcinoma arising in the wall of a cyst is a rare occurrence when considering all types of breast lesion, it is not so excessively rare when we consider solitary lumps of doubtful nature clinically—just those lumps in fact for which the diagnostic acumen of the exploring needle is most required. The recovery of clear fluid from the aspirating needle in these lesions is diagnostically misleading.
>
> " With regard to treatment, aspiration must be considered equally unsatisfactory. The removal of the contents of a cyst will give gratifying results only when in any case the cyst was in the state in which absorption was taking precedence over accumulation, and one therefore in which spontaneous disappearance was likely in the course of time. Furthermore, it has no effect at all on adjacent smaller and unpenetrated cysts, which are left to grow and to cause annoyance and anxiety subsequently.
>
> " This is not to say that in the majority of cases aspi
> will not yield the correct diagnosis, but so will a ca
> clinical examination, and aspiration is not much of an imp
> ment on this ; nor is it to deny that in many cases aspir
> will *cure a cyst* ; but the difference in disturbance to
> patient between aspiration and removal is so trivial and
> difference in certainty of diagnosis and to a less exte
> success in treatment is so great that the operation
> *nearly always* be preferred."

I shall of course keep an open mind about *this ma*
but at present, and while conceding that it is a
measure in expert hands, I am doubtful whether
one that should be widely taught, since any misi
pretation of the teaching might be disastrous.

Department of Surgery,
Guy's Hospital, London, S.E.1.

H. J. B. ATKIN

PROCAINE PENICILLIN AND BREATHING EXERCISES IN POSTOPERATIVE PULMONA COMPLICATIONS

SIR,—May I congratulate Dr. Palmer and Dr. Se
(Feb. 16) on their statistical approach and on t
unassailable conclusion that their results " provide
evidence that procaine penicillin and breathing exer
. . . reduce the risk of postoperative pulmonary com
cations." However, in their summary (too often all
is read) they state that penicillin and breathing exer
did not significantly reduce the incidence of these c
plications. I submit that this is an altogether diffe
contention which cannot rest upon the evidence presen

Out of the whole series of 160 patients submitted
hernia operations, 26 (16·25%) developed chest trou
For a sub-group of 38 I make the standard error of
centage to be 6. Therefore on chance alone it would
expected that not uncommonly as few as 2 or as man
10 patients in a random sample of 38 might develop
complications. In fact, of the group of 38 who rece
penicillin and breathing exercises (for example) 7 su
quently had these complications. Therefore it is not
improbable that the treatment given actually redu
the incidence in this group 30% below what it m
otherwise have been.

The question " Do penicillin or breathing exer
reduce the risk of postoperative pulmonary comp
tions ? " must surely, if my calculations are corr
remain open for the present ; for it would *not app*
that the evidence presented has given *statistically* v
support one way or the other.

London, W.1.

H. DAINTREE JOHNSO

INJECTION ROUTINE IN OPERATING-THEAT

SIR,—Major-General Dimond and his colleagues (
23) are to be congratulated on their detailed invest
tion into the hazards in the use of drugs in operat
theatres. While I would agree with most of t
observations, I must disagree with some of t
conclusions.

It is significant that the first cause of accidents m
tioned in the article is given pride of place : " (*a*) Fail
to read or check the label." This perhaps should h
been printed in bolder type, because its lesson appe
to have been missed by the authors. For instan
another cause of accidents is stated to be : " (*h*)
use of *gallipots of similar appearance* . . ." Is *this*
the same risk in a different guise ? Surely the risk
the use of gallipots is *not* the similarity in appeara
but the fact that almost in [illegible] labell
There is of course the [illegible] wh
appears to be intended, that gallipots should be dissimi
in appearance, and that the theatre staff should
encouraged to recognise a potent substance, not
reading a label, but by the distinctive shape of a contain
Multiple-dose containers—" their use in operatin
theatres should be prohibited " (suggestion 12)—app

o be criticised for the same reason, that they are ndistinguishable in shape from one another.

It is not without good reason that a pharmacist stores range of potent drugs in containers of similar appearnce, so that he is forced to recognise a drug by the only afe method—namely, by reading a label. There is no other short cut to the safe handling of drugs.

I submit that if containers for injectable drugs were imilar with no other distinguishing features than the wording of the labels, and that if the theatre staff were trained to read, re-read, and check labels, most of the hazards would disappear.

For similar reasons the suggestions 6, 7, 13 (*a*), (*b*), and (*c*), and 14 are to be deplored. Just as the shape of a container should not be an aid to drug recognition, so too the use of diagnostic colours for containers or solutions should be avoided. Incidentally if a colour recognition scheme for potent drugs is recommended, should the risks arising from colour-blindness among the theatre staff be ignored ?

The plea by General Dimond and his associates for concise, legible, but indelible labels on ampoules is well founded.

W. TRILLWOOD
Director of Pharmaceutical Services.

United Oxford Hospitals.

AN UNUSUAL EPIDEMIC

SIR,—Epidemics of acute labyrinthitis described by your correspondents remind one that in 1927 Dr. R. I. Poston,[1] of Manchester, described some cases of epidemic encephalitis which showed this picture on its own, and others in which it was found with the usual signs—oculomotor paresis, increased salivation, &c.—of the essential disease. In addition to the vertigo he described spontaneous as well as induced nystagmus.

Dundee.

J. A. R. BICKFORD.

B.M.R. AND RADIO-IODINE TESTS IN DIAGNOSIS OF THYROID DISEASE

SIR,—There is a wide divergence of authoritative opinion on the relative value of estimations of radio-iodine uptake and of basal metabolic rate in the diagnosis of thyroid disease. The table shows the ranges of values given in two recent papers, one from the Mayo Clinic (Keating et al. 1950) and the other from this country (Goodwin et al. 1951).

Group of thyroid dysfunction	No. of cases	Percentage of cases in normal range		
		Basal metabolic rate	Radio-iodine	
			Urinary excretion	Thyroid uptake
Keating et al. ..		(−13 to +13%)*	(48 hr.)	(24 hr.)
Exophthalmic goitre ..	123	4·8	5·7	18·0
Toxic adenoma ..	25	8·0	48·0	38·4
Myxœdema	46	13·0	76·1	39·3
Goodwin et al.		(−20 to +20%)†	(24 hr.)	(24 hr.)
Primary thyrotoxicosis	33	27·0	24·0	0
Toxic adenoma ..	11	55·5	54·5	0
Myxœdema	4	50·0	100	25

* Mayo Clinic standards. † Standards not stated.

Basal Metabolism

Goodwin et al. say of the B.M.R. that "our figures show clearly its relative unreliability as a diagnostic method." Their grounds for this conclusion are as follows :

(1) They could not get reliable results.

(2) Keating et al. (1950) found that only 49% of euthyroid patients (i.e., with no thyroid disease) had a B.M.R. within the Mayo Clinic normal range of +13 to −13%.

(3) "In some cases a normal B.M.R. was found in the presence of severe thyrotoxicosis"; they quote Bartels (1950) as supporting this observation.

(4) A raised B.M.R. is found in pyrexia, heart-failure, and anxiety states.

Let us study their premises seriatim.

(1) *Their Own Observations.*—Goodwin et al. state that by their technique normal people may give readings between +20 and −20%. They do not say what standards they adopted, and there are several different ones to choose from, which would give quite different values for the B.M.R. Whatever standards they used, however, a range of +20 to −20% for normal people clearly indicates errors in technique. Having adopted this range as normal, it is not surprising that they were confused by their findings in patients with overactivity and underactivity of the thyroid gland.

(2) *Observations of Keating et al.*—Goodwin and colleagues do not explain why Keating et al. found that as many as 51% of their 146 euthyroid patients had a B.M.R. outside the range of +13 to −13%. This is the reason. In 1936 Boothby et al. studied the B.M.R. of 639 healthy males and 828 healthy females, and found that 95% fell within the range +13 to −13% ($\overline{m} \pm 2\sigma$). Keating et al. deliberately selected their 146 euthyroid patients from those with diseases in which the B.M.R. might well lie outside normal limits ; and they made this quite clear in their paper. Conditions other than thyroid disease can, of course, raise or depress the B.M.R., but this will be referred to below.

(3) *Bartels's Observations.—It is true that Bartels (1950)* found B.M.R.s of +13% and +10% in two clinically severe cases of thyrotoxicosis. But Goodwin et al. do not mention Bartels's statement in the same paper that iodine medication reduced the B.M.R. to −10 and −13% respectively, indicating at least 23% toxicity in each case. Bartels concluded that "the B.M.R. is especially informative when utilised to ascertain the response to antithyroid therapy."

(4) *B.M.R. in Pyrexia, Heart-failure, and Anxiety States.*—The conditions other than thyrotoxicosis that may raise the B.M.R. include leukæmia, polycythæmia vera, the active stage of hyperpituitarism, Cushing's basophilism, heart-failure with dyspnœa, pyrexia, the last months of pregnancy, and perhaps aortic stenosis. If a clinician suspects thyrotoxicosis he has presumably excluded these other conditions. However, in doubtful cases (e.g., ? thyrocardiac disease), the administration of iodine or iodides will cause a significant change in the initial B.M.R. if thyrotoxicosis is present (Means 1933, Robertson 1934) but not in any other condition. As Du Bois pointed out in 1921, fever raises the B.M.R. 7·2% for every 1°F above normal, so a simple correction could be made for this. Heart-failure does not raise the B.M.R. unless dyspnœa or thyrocardiac disease is present. Anxiety states do not raise the B.M.R. ; I agree with Keating et al. that the apparent rise is due to poor tests and non-basal conditions. Basal conditions can be obtained with patience.

From the B.M.R.s in the table it will be seen that there are serious discrepancies between the results reported from the Mayo Clinic and those of Goodwin et al. I have had some practical experience of variations in the B.M.R. in thyroid disease for over twenty years, and my figures agree well with those of Keating et al.

Radio-iodine Tests

After condemning the B.M.R. as unreliable from *their own* figures Goodwin et al. proceed to eulogise radio-iodine tests as follows :

> "We feel that if the necessary equipment is to be obtained and used, it is worth while investigating every patient as fully as possible. From such a study of the different aspects of thyroid function the most accurate deductions can be drawn regarding the degree of over- or underactivity of the gland. There will always be patients about whose thyroid function the clinician remains in doubt even after the fullest clinical and laboratory investigation. If their iodine metabolism is investigated by the isotope technique valuable additional information is obtained, and great reliance can be placed on the results."

I cannot speak from personal experience of radio-iodine tests in thyroid disease, but the table again shows some discrepancies. The two groups of observers agree on the reliability of radio-iodine tests in primary thyrotoxicosis (exophthalmic goitre), but Goodwin et al. can claim from their figures that it is absolutely specific, whereas Keating et al., with their larger series, could not do so. The Mayo Clinic workers in fact reported two cases of severe exophthalmic goitre in which there was no accumulation of radio-iodine in the thyroid, though they could not certainly exclude the presence of interfering substances such as iodine. Just as iodine administration can confuse the interpretation of a B.M.R., it can render a radio-iodine test useless. Moreover, Keating et al. found false-positive tests in adenomatous goitre without hyperthyroidism, and in colloid goitre.

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[1] See *Lancet*, 1927, i, 438.

In the diagnosis of toxic adenomatous goitre, Keating et al. found radio-iodine tests of limited value at best, however they were done; between a third and half of their cases fell within the normal range. Goodwin et al. have obtained quite a different picture—in all their cases the findings were outside their normal range, indicating that the radio-iodine test is also specific in toxic adenoma.

As regards hypothyroidism, Keating et al. concluded that radio-iodine was not of much diagnostic value because there was a considerable overlap into the normal range; furthermore, patients with acute thyroiditis, Riedel's thyroiditis, simple goitre, cardiac decompensation, renal disease, and Addison's disease had a reduced radio-iodine uptake like some cases of hypothyroidism. Goodwin et al. give no details of the findings in hypothyroidism. They say in their discussion that the degree of thyroid underactivity can be accurately estimated from the radio-iodine findings, but in fact their figures (see table) support the view of Keating et al.

Radio-iodine Tests v. *B.M.R.*

Since Magnus-Levy first demonstrated a raised B.M.R. in thyrotoxicosis in 1895 the test has passed through periods of acclamation and periods of condemnation. It is natural to compare the newer radio-iodine test of thyroid function with the old-established estimation of B.M.R. The main criticisms of the B.M.R. as a diagnostic aid are too well known to require repetition. From their comprehensive study of radio-iodine diagnostic tests, Keating et al. reached these conclusions (my italics):

> "It appears that interpretation of radio-iodine tests is beset with fully as many pitfalls and complexities as is the interpretation of the B.M.R., even though they are different in kind. Our experience with radio-iodine has not led us to the conclusion that it is any more sensitive or more specific, or less subject to technical error or misinterpretation, than the B.M.R. *Moreover, with present techniques radio-iodine tests have one important disadvantage; they expose the patient to considerable quantities of radiation.* Both on this account and because of the difficulties enumerated, we should prefer the B.M.R. to a radio-iodine tracer if we were compelled to rely on only one diagnostic procedure."

In the face of these views, Goodwin and his colleagues dismiss the B.M.R. as an unreliable diagnostic test, primarily because they themselves found it of little help.

Some years ago a distinguished surgeon told me he had a patient with severe thyrotoxicosis who had lost 36 lb. in weight in a year and yet had a B.M.R. of −22%. He was intending to publish these rare findings, so I asked if I might see the patient and confirm the B.M.R. reading. I found a typical case of exophthalmic goitre, with a B.M.R. of +41% (Aub-DuBois standards). When I came to inspect the case-notes and "B.M.R. report" I found that the patient's respiratory quotient was recorded as 0·55—an impossibly low figure, except perhaps in the hibernating marmot, which is assumed to be converting fats into carbohydrate (Lovatt Evans 1949).

There are plenty of pitfalls in the measurement, clinical application, and interpretation of B.M.R.s; but it does not necessarily follow that the test is unreliable. The B.M.R. can be relied on if it is properly done; this calls for patient attention to detail, a knowledge of the pitfalls, and a close watch for the aforesaid pitfalls, and a full knowledge of how to avoid them.

The London Clinic,
W.1.

J. DOUGLAS ROBERTSON
Director,
Department of Clinical Investigation.

REFERENCES

Bartels, E. C. (1950) *J. clin. Endocrinol*, 10, 1126.
Boothby, W. M., Berkson, J., Dunn, H. L. (1936) *Amer. J. Physiol.* 116, 468.
Du Bois, E. F. (1921) *J. Amer. med. Ass.* 77, 352.
Goodwin, J. F., Macgregor, A. G., Miller, H., Wayne, E. J. (1951) *Quart. J. Med.* n.s. 20, 353.
Keating, F. R., Haines, S. F., Power, M. H., Williams, M. M. D. (1950) *J. clin. Endocrinol.* 10, 1425.
Lovatt Evans, C. (1949) Principles of Human Physiology. 10th ed., London; p. 944.
Magnus-Levy, A. (1895) *Berl. klin. Wschr.* 32, 650.
Means, J. H. (1933) *Ann. intern. Med.* 7, 439.
Robertson, J. D. (1934) *Lancet*, ii, 1076.

UNDERFEEDING AS A FACTOR IN INFANTILE VOMITING

SIR,—I agree with much that Dr. Wood says in his article of Jan. 5.

When no obvious cause can be found for vomiting in infants we are perhaps too inclined to regard this symptom as of "unknown origin." Air-swallowing certainly may cause colic and vomiting, but air-swallowing itself may be due to several different causes—technical mistakes in breast or artificial feeding, anatomical defects, gluttony, and perhaps hunger. Furthermore, when a baby is constipated, fails to gain weight properly, has slight signs of dystrophy, and is quiet, is that baby "hungry"? He is getting too little food—the weighing-scales will confirm that—but he is not hungry. On the other hand, some babies whose weight increases satisfactorily on a carefully calculated and copious diet show distinct symptoms of "hunger," such as crying and finger-sucking. We must also distinguish vomiting due to underfeeding from underfeeding due to vomiting.

Hilversum, Holland.

D. P. R. KEIZER.

TOXICITY OF DIHYDROSTREPTOMYCIN SULPHATE

SIR,—We are grateful to Dr. Hawkins for pointing out (Feb. 16) the misunderstanding about the purity of the dihydrostreptomycin sulphate in use in the United States in 1950.

This misapprehension was due, not to any confusion on our part between purity and purity expressed as potency, but to the fact that the expression used in the article we quoted—"mcg. per milligram"—was taken by ourselves (and by authorities whom we consulted) as meaning, as applied to dihydrostreptomycin sulphate, mcg. of dihydrostreptomycin sulphate per milligram. It now transpires that the expression in fact means mcg. of dihydrostreptomycin *base* per milligram. Thus, as Dr. Hawkins points out, the purity of the commercial dihydrostreptomycin sulphate available to the U.S.A. was nearly 91%, and not 72·5%.

This correction has to be applied to only one series of cases we cited from published reports—that of Glorig, Romansky, and Katz—and when applied it confirms our results, in that the purity of the dihydrostreptomycin sulphate they used and found to produce deafness was even greater than that used in our investigation.

Dr. Hawkins also considers that we have given a "partially erroneous account" of his work, and supports this by stating (erroneously) that he is quoted "as having found that both streptomycin and dihydrostreptomycin sulphate have little effect on the auditory nerve," and by showing that he, in fact, demonstrated that vestibular function was abolished in cats receiving streptomycin and was disturbed in those receiving dihydrostreptomycin, and that cochlear function was depressed by streptomycin in very large doses, and not by dihydrostreptomycin sulphate. From Dr. Hawkins's account it would indeed appear that we had given an roneous impression of his work; but he is under a isapprehension, revealed by his mistaken addition f the phrase "on the auditory nerve," which did not ccur in our work. We were concerned at that stage f our paper with the toxicity of dihydrostreptomycin r the hearing, and left it to be inferred that we meant ffects on the hearing of his cats; we did not mean, and ertainly did not say, effects on the auditory nerve (i.e., n the vestibular apparatus as well). We may add that e did not profess to give an account of Dr. Hawkins's ork, but only to draw attention to his conclusion that he toxicity of dihydrostreptomycin might be attributed o impurities contained in it.

Dr. Hawkins's criticisms in no way invalidate our nvestigation or its conclusions, which were that dihydrotreptomycin sulphate as it is generally supplied in this ountry (88% pure, as we stated) appears liable to roduce nerve deafness.

Finally, we cannot agree with Dr. Hawkins that 'it is perhaps a counsel of perfection to urge that no ihydrostreptomycin should be used unless its potency pproaches the theoretical maximum." There is a reat deal of clinical evidence that dihydrostreptomycin f purity up to 90% may produce serious deafness as side-effect. Should this be due to the dihydrostreptomycin itself, the drug obviously should be stopped, particularly with so efficacious an alternative as streptomycin easily available; the only excuse for persisting with the drug is that impurities may, as Dr. Hawkins postulates, be responsible; in which case it is surely no counsel of perfection, but mere common sense, to discontinue the clinical use of the drug until maximum purity is obtained and this highly purified substance is conclusively shown to be free of liability to produce nerve deafness.

University College Hospital,
London, W.C.1.

CONWAY DON
JOAN GREGORY.

INDUSTRIAL HEALTH SERVICES

SIR,—I would like to add something to Dr. Herford's comments (Feb. 23) on Dr. Parker's letter of Feb. 9.

Dr. Parker appears to be unaware of the fact that the practice of industrial medicine is something much more than the practice of industrial hygiene. It would perhaps clarify the issue if I were to set out shortly the categories into which the work of an industrial medical officer falls. These are:

1. Work which requires little detailed knowledge of the industry—e.g., (*a*) the supervision of first-aid arrangements; (*b*) simple hygiene of the public-health type; and (*c*) the treatment of medical and surgical emergencies arising at work.

2. Work which requires specific knowledge of the industry—e.g., (*a*) pre-employment examination; (*b*) rehabilitation and the settling into suitable jobs of men temporarily or permanently disabled; and (*c*) specific industrial hygiene (that is, advice to management on the specific hazards of existing and projected processes).

Now it is quite true that a medical officer of health is competent to carry out the first class of work; and indeed, as Dr. Parker says, much of it is already his statutory responsibility, though this responsibility is not always recognised. Work in the second category, however, is not fully within the competence of the medical officer of health, or of any other doctor, unless he has the time and the inclination to learn a good deal about the industry in which it is carried out.

There are few things more irritating to a man in control of a factory than to get medical recommendations based on inadequate knowledge of the industry. Such recommendations often cannot be carried out, and only discredit industrial medicine in general and the doctor who makes them in particular.

It is quite true that an officer of the public-health department could learn about one or more industries; but he would need to be a very exceptional man if he were to learn about all the industries in even a moderately busy industrial town. Yet to learn about even one industry requires time and interest, and it is doubtful if medical officers of health as a class have both. It would be interesting to know how many medical officers of health take seriously their statutory responsibility under the Factories' Act.

I am well aware that the industrial medical services as at present constituted leave the bulk of industry without any effective industrial medical service, and that the vast majority of factories are too small to support a full-time medical officer. The problem will not be solved, however, by laying upon the medical officer of health additional responsibility for which he is not equipped, in a field in which he has so far shown little interest.

London, N.1. INDUSTRIAL MEDICAL OFFICER.

HAYGARTH HOUSE, HARLOW

SIR.—In his thoughtful letter (Feb. 9), Dr. Atkinson raises two points of importance. By implication he criticises the Harlow health centre for its "unambitious" contents, and for not having medical, or at least nursing, aid continuously available in the building.

The contents of any health centre must be related to other facilities available in the neighbourhood. Harlow is no "housing estate," but a town in embryo; before many years are past it will have a population of 80,000 and a general hospital of 600 beds. It will be possible to reach this hospital from any point in the town within a quarter of an hour. As a first stage, an outpatient department will be built; I have no doubt that this will follow the good example of adjacent regional hospitals by providing open access for general practitioners to pathology and radiology services. Whether Harlow has four large health centres or ten small ones, it would be uneconomic, to say the least, to set up casualty departments, pathology laboratories, and radiology units at the health centres as well. I hope, however, that we may experiment with simple pathology and physiotherapy in some, at least, of the health centres.

Dr. Atkinson describes the Harlow health centre as a "new type lock-up surgery," with the doctors "living outside the area of their practice." If his objections on this score are valid, they strike at the whole idea of group practice conducted from a central point where a number of doctors work together. Such practices are already the rule in many of our smaller towns, and in my experience they are both efficient and popular.

Unless a junior partner or assistant is housed in a flat over the premises, such group-practice centres are not as a rule manned medically outside surgery hours. During the day there is a secretary to take messages, while at night one or two doctors are always available on the telephone for emergencies. These arrangements work well, and to keep a doctor hanging around a health centre or group-practice centre out of hours in case an emergency should turn up seems most wasteful.

As against these arrangements, I cannot see the added virtue of putting these same doctors each into a separate surgery. In consequence, some would probably be without secretaries; out of hours the patient could only rely on finding his doctor in at meal-times; this is a poor kind of emergency service.

If Dr. Atkinson is protesting at the doctor who lives five miles away from his lock-up surgery in an industrial slum, who answers his telephone and his emergency calls slowly and unwillingly, then I see his case. At Harlow our first doctor lives within 600 yards of the health centre, and his future colleagues cannot in the nature of things live much more than twice this distance away. The patients already know the doctor's house and telephone number; they know that his emergency kit is in his car; but they also know that in anything but a real emergency he can give them better service at Haygarth House, where he can examine them at leisure in a good light.

Finally, there is no question of working the health centre like a "public-health clinic." The aim is rather to conduct the public-health clinic like a friendly general practitioner's surgery. Indeed, one early patient remarked: "I did not think I was going to like these health centres; I thought they would be so impersonal; but here it is quite different."

London, N.7. STEPHEN TAYLOR.

FRONTAL LOBES OF THE HUMAN BRAIN

SIR,—In your very welcome annotation of Feb. 23 you ask: "When are we therefore ethically justified in advising a procedure which, though it relieves the misery of neurosis or of pain, will also dull the patient's sense of responsibility, conscience, and feeling for others?"

The ethics of leucotomy is now being officially brought into discussion, and this seems a good moment to make clear the attitude of the Board of Control. I have heard it said that these matters can safely be left to the Board of Control, and for this reason I have asked for a statement which can be quoted. I received this reply:

> "The Board . . . do not consider it as any part of their functions to express an opinion concerning the ethics of leucotomy. As regards the evaluation of leucotomy as a form of therapy the Board take the view that this is a matter for those branches of the medical profession which are concerned with the performance of the operation."

From this it will be seen that ordinary medical opinion and public opinion in general must be made clear to the neurosurgeons and to the psychiatrists with whom they work. Quite rightly the problem cannot be left to the Board of Control, but belongs to us as individuals.

London, S.W.1. D. W. WINNICOTT.

TREATMENT OF SCLERODERMA[1]

SIR,—The report by Dr. Briggs and Professor Illingworth (Feb. 16) of the failure of A.C.T.H., sodium *p*-aminobenzoate (P.A.B.A.), and 4-3-hydroxy-2-phenyl-cinchoninic acid (H.P.C.) in a case of scleroderma prompts us to record our recent experiences in the treatment of this condition.

CASE 1.—Man, aged 57. Extensive scleroderma of 18 months' duration involving face, neck, forearms, hands, and feet (acrosclerosis). No radiological evidence of pulmonary or œsophageal involvement; persistent albuminuria. Treated with H.P.C. 1·5 g. daily for 6 weeks. There was prompt subjective improvement and a sensation of well-being, but no objective change could be detected clinically or histologically. The patient died at home in uræmia 6 months later, the scleroderma remaining unchanged during this period. No post-mortem examination could be arranged.

CASE 2.—Woman, aged 57. Extensive scleroderma of 3 years' duration involving arms, forearms, and hands, lower legs, and abdominal wall. Some features of dermatomyositis were associated. Treatment with H.P.C. 1·5 g. daily for 3 weeks produced no objective improvement.

CASE 3.—Woman, aged 46. Severe involvement of face, neck, hands, and feet (acrosclerosis), steadily progressive for about 11 years. Cortisone 100 mg. by intramuscular injection daily for 10 days produced very definite subjective and objective improvement. There was increased mobility of the fingers and face. The patient was able to carry out movements which had been impossible for at least 2 years.

CASE 4.—Woman, aged 46. Moderately severe involvement of face, neck, shoulders, hands, and feet of 3 years' duration. Treatment with cortisone by intramuscular injection 50 mg. on the 1st day and 100 mg. daily for 9 days produced definite subjective and objective improvement. The upper limit of sclerodermatous involvement of the forearms retreated 3–5 cm. on extensor and lateral aspects, and there was increased mobility of the fingers. She was also able to dorsiflex the hand for the first time in many months.

Although there seem to us to be no good grounds for considering that the sclerodermatous process in the acral type of scleroderma is essentially different fr generalised morphœa, our first two cases may not strictly comparable with those in which Rennie et obtained promising results with H.P.C.

Kierland and Hines[2] reported definite remission symptoms in four patients with scleroderma treat with cortisone. They claim that although sympto reappeared after a few weeks, the same degree of improv ment was produced in less time with a smaller total d in subsequent courses of cortisone. Although Whittl observed no benefit in one case, cortisone seems to us give more encouraging results than any treatment have previously employed.

Department of Dermatology,
United Cardiff Hospitals.

A. J. ROOK.
W. FRAIN-BELL.

ECONOMY IN HOSPITALS

SIR,—Your observations under this heading last wee are most pertinent, particularly those relating to t cost of travelling time and the payment of travelli expenses. This is well illustrated by the followi figures from a London hospital:

> There are just over 200 beds. 64 members of the part-tir staff are paid £11,000 per annum for travelling time an £2100 per annum for mileage.

Further comment on this is unnecessary when so muc emphasis is being placed on small economies elsewhere i *the hospitals.*

Domiciliary visiting under the National Health Servic is developing in a most interesting way. There ar numerous variations in its use and abuse from on region to another. Whole-time consultants are not pai for visiting, and I believe that any abuse could b eradicated if part-time consultants were asked to accep payment for consultations on a basis proportionate t sessional contracts held—i.e., those holding contract for $5^1/_2$ sessions weekly would be paid for half the visit undertaken.

The majority of consultants hold their full number o weekly sessions ($9^1/_2$), and it is true that some of them hold contracts for 14 or more sessions weekly. In one region it is stated that a part-time tuberculosis physicia only sees patients in their own homes if he is paid fo a domiciliary visit each time.

The beam in our own eye is only too obvious to man lay observers.

SCRUTATOR.

MEDICINE WITHIN THE ATLANTIC COMMUNITY

SIR,—Dr. Meiklejohn (Feb. 16) deplores the relativ lack of interchange of personnel between the U.S.A. and ourselves, and quotes the few examples known t him where arrangements already exist. He will, therefore, be gratified to know of one more.

Through the good offices of Dr. E. D. Churchill there has developed a system of exchange between the Massachusetts General Hospital and the Birmingham teachin hospitals. Two of us received from Dr. Churchill formal invitations each to spend one month working with the residents on his surgical service. Last autumn Dr. Churchill came to us for a month as visiting professor, and all, senior staff and students alike, gained greatly from the impact of his visit; and next autumn we look forward to welcoming the professor of medicine from the Massachusetts General Hospital, too. We also hope to receive from Harvard the first of the younger men of registrar grade. During the past eighteen months no less than 8 of our clinicians have spent times varying from six weeks to eight months in American centres and others have expressed their wish to do likewise.

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1. Rennie, J. B., Milne, J. A., Sommerville, J. *Brit. med.* 1951, i, 383.
2. Kierland, R. E., Hines, E. A. *Arch. Derm. Syph.* 1951, 6 549.
3. Whittle, C. H. *Brit. J. Derm.* 1952, 64, 29.

All this has been made possible through the hospital dowment fund, part of the interest on which is directed wards medical education and research. Most, of urse, is spent on the latter, but the committee advising e board on the disposal of this money feels very strongly at one of the most educative and stimulating experi-ces open to clinicians is to see the work of other untries, and especially of American centres; to take rt in discussions; and, above all, to meet the men hose papers they have read.

F. A. R. STAMMERS

Department of Surgery,
University of Birmingham.

Chairman, Endowment Fund
Research Committee.

AN UNUSUAL SKIN CONDITION

SIR,—In your issue of Feb. 23 you report a "small itbreak of a puzzling dermatological affection." (But re "at least 200 cases" to be sneezed at ?) The descrip-on of this affection closely resembles keratosis follicularis ontagiosa, a disorder to which Brooke, of Manchester, rst drew attention in 1892. A section is devoted to it in *iseases of the Skin* by Sutton and Sutton (10th ed., 939, vol. I, p. 578).

University College Hospital,
London, W.C.1.

W. N. GOLDSMITH.

PSYCHOSOMATIC SYMPTOM FORMATION

SIR,—I have studied Dr. Macalpine's article of Feb. 9 ith great interest and enjoyment.

Precipitating factors, as Dr. Macalpine remarks, have een far too much emphasised; indeed the absence of ny obvious precipitating factor, such as death of a love bject or defeat in some life situation, has commonly een regarded as of diagnostic value in deciding whether r not certain conditions were psychosomatic. Precipi-ating factors have two aspects—namely, the overt reality rauma, and the latent aspect. The second is always nore important, and cannot be delineated without psychological insight.

Dr. Macalpine states that in psychosomatic illnesses secondary gain is inconspicuous or absent. Here I cannot easily agree. It is my experience that in asthmatics, and also in peptic ulcer patients, the psychosomatic symptom is often exploited by the patient, mainly to dominate in some way people in his environment.

Dr. Macalpine suggests that the therapist's main task is to discover which emotion is being expressed in the symptom. This implies two things: firstly, that all psychosomatic symptoms are merely aberrant expressions of emotion; and secondly, that emotions differ fundamentally and in their somatic equivalents from one another. I have already suggested that the view that psychosomatic symptoms were based purely on emotion was erroneous.[1] Dr. Macalpine has emphasised the importance of conflict, and will therefore agree that all psychosomatic symptoms ultimately arise from unconscious conflict, as indeed does all morbid emotion (e.g., anxiety). Is Dr. Macalpine sure that psychosomatic symptoms always are anxiety equivalents ? Is it not true that libido, as opposed to emotion, is commonly displayed through psychosomatic symptoms, just as it is in psychoneurotic symptoms ? Emotion cannot occur per se, but is always related to the driving of unconscious forces. It is quite true, in my experience, that much patient work must be spent with patients to enable them to see the relationship between their symptoms and latent anxiety. Is this specific to the psychosomatic illness ?

Dr. Macalpine also suggests that palpitation is a physical concomitant of anxiety. I have come to doubt whether this is the whole story. Patients have told me that it is not the tachycardia that is distressing, but the awareness of it. In other words, "heart consciousness" is intensely distressing, whereas tachycardia is frequently unnoticed.

Dr. Macalpine's clinical observations are all on cases of skin disease. The skin is not entirely comparable with all other organs which show psychosomatic manifestations. The skin is the "outside," and many other organs constitute the "inside." My short experience of skin lesions suggested to me that some at least were clearly demonstrative. They were there to be seen; and the patient exhibited them, often as a protest, and often as an admission of guilt (e.g., rosacea). Whilst it is quite true that remarkable results can be obtained in psychosomatic skin disorders by abreaction techniques, this does not prove that emotion is the only factor in their production. In my submission, conflict remains.

Dr. Macalpine apparently does not fear a complication which has exercised my mind. I believe that it is possible to convert by psychotherapy a psychosomatic disorder into an anxiety state. I have had to ask myself, with which condition is the patient better off ? Anxiety states are neither easily resolved nor easily borne, and a patient with a neurodermatitis of the neck may well be better off to keep it, unless one is prepared to embark on the major psychotherapeutic procedures which states of anxiety demand.

One further point arises. The "miracle cure" which occasionally follows "one or two" interviews with a psychotherapist, is relatively common in skin disease. I have not always found that this improvement was necessarily preceded by the abreaction of emotion. In fact, it sometimes takes place when very little of an emotional nature has occurred in the therapeutic situation. I suspect that these occurrences are related to a redistribution of libido consequent upon the establishment of a psychotherapeutic rapport. Indeed, this is the basis of my disagreement with Dr. Macalpine's views. I cannot accept her statement that "the psychosomatic symptom is a rudimentary, disguised, and only partially expressed emotion, somatically displayed without awareness of its significance." I suggest, on the contrary, that psychosomatic symptoms are, like psychoneurotic symptoms, related to unconscious conflicts, and that what they seek to express is not emotion but libido. Further, that there is a distinct danger that reducing the patient to the recognition of his underlying anxiety, without reducing him to an insight into the underlying conflicts, may be a disservice and therapeutically undesirable.

Wanstead Hospital, London, E.11.

D. H. IRWIN.

SIR,—From an official report I once extracted the phrases "nervous instability," "neurasthenic temperament," "nervous disposition," "permanent nervous weakness," "nervousness of temperament," and "nervous type." I have also met neurasthenia, neuropath, psychoneurosis and neuropsychosis, neurosis and neurotic, neural exhaustion, nervous debility, nervous exhaustion, nervous breakdown, neuromimesis, and cerebro-cardiac neuropathy.

I present these physiological fantasies in the hope that the list will help to kill that over-ripe catch-phrase "psychological jargon" which Dr. Hall Ratcliffe drags into his letter in last week's issue.

St. Albans, Herts.

MILLAIS CULPIN.

HICCUP DURING ANÆSTHESIA

SIR,—I, too, have found that during upper abdominal surgery hiccups are quite common when the anæsthetic sequence is thiopentone, nitrous oxide, oxygen, and curare, whereas if curare is combined with more potent inhalation drugs, and the level of general anæsthesia is deeper, this complication is rare. Therefore I agree with Dr. Hendrie and Dr. Kaufman (March 1) that the onset of hiccups is related to the depth of anæsthesia. Similarly, hiccups may suddenly occur in these abdominal cases during controlled respiration that has been established mainly with curare and hyperventilation with nitrous oxide. It is seldom seen, however, when the respiration is controlled with curare/cyclopropane anæsthesia. In my experience hiccups are not necessarily initiated by any particular intra-abdominal manœuvre, and the required level of anæsthesia must be maintained throughout operation.

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1. *Lancet*, 1951, i, 348.

It is well known that in upper abdominal operations the level of anæsthesia must be deeper than in the majority of intrathoracic cases, which can be easily and smoothly anæsthetised with thiopentone, nitrous oxide, oxygen, and curare, any excessive diaphragmatic movement being readily controlled with additional curare.

I was interested to read of the use of 'Methedrine' (Dr. Fajardo, Feb. 2) and the vapour of amyl nitrite (Dr. Lee, Feb. 16) in the treatment of hiccups; but I feel that in view of the cardiovascular effects of both drugs every effort should be made to avoid the onset of this embarrassing condition.

London, E.C.1. ROBERT I. W. BALLANTINE.

THE LIVER AND ENDOCRINE DYSFUNCTION

SIR,—In your leading article of Feb. 16 you write: "Zondek showed that in vitro the liver inactivates 80–90% of added œstrogen." Actually the inactivation of œstrogens by liver tissue was discovered by F. Silberstein,[1] late professor of experimental pathology in Vienna and now pathologist at the National Temperance Hospital, and his associates one year before Zondek's publication.

Pathology Department,
Children's Hospital, Birmingham. *H. S. BAAR.*

CAT-SCRATCH FEVER

SIR,—Dr. Willcox's letter last week contains two statements which are of particular interest. He says that the skin-test antigen prepared by Professor Mollaret from cat-scratch material (lymph-nodes) "will give cross positives with members of the psittacosis/lymphogranuloma-venereum/trachoma group." He further says that non-specific urethritis "is believed to belong to this group of virus diseases" (psittacosis/lymphogranuloma-venereum group). Would it be possible for Dr. Willcox to give the evidence in support of these statements? I am asking for it in this way because I feel sure that there are others interested in this group of viruses who have been following this correspondence and who, like myself, would like to have Dr. Willcox's evidence on these two points.

London Hospital, E.1. S. P. BEDSON.

MERCURY AND PINK DISEASE

SIR,—With reference to last week's article by Dr. Holzel and Dr. James, I doubt whether these workers are correct in assuming that the 61 cases of pink disease treated in Manchester hospitals during 1950 give a complete picture of the incidence of this disease.

In a small inquiry at Darlington last year, of 25 patients who had suffered from this malady since 1945 only 6 had been admitted to hospital. As the danger of cross-infection is particularly great in such cases, and the need for continuous care and attention outstanding, it would seem probable that physicians would recommend treatment at home whenever conditions there were at all propitious. Though the Darlington series was too small to provide statistically significant conclusions, it was found that the home circumstances of patients were on the whole above average; like poliomyelitis, pink disease seems not to be a disorder of the poor.

In populous areas, such as Manchester and Salford, where this illness is common, the various health departments might consider making further inquiries as to total incidence and sociology. As much (if not more) is likely to be learned about the source, and hence about the prevention, of a disease from the normal environment and condition of the patient as from observations in the ward and the laboratory.

JOSEPH V. WALKER
Darlington. Medical Officer of Health.

Parliament

Housing the Elderly

IN the debate in the House of Lords on Feb. 26 Lord AMULREE pleaded for more houses for the elderly and infirm. Care should be taken not to put up houses for old people in too large colonies. What was needed in this country was to get the old people distributed so that they could give help and comfort to their children and to young members of the community generally. If people were properly housed he believed that there would be a big reduction in the incidence of the chronic rather degenerating and crippling diseases which sometimes attended old age. One of the real tragedies of the present time was the separation of housing from health. Housing, properly directed, could be of immense value to curative and preventive medicine.

The ARCHBISHOP OF YORK said that overcrowding in our towns was almost as serious as it ever had been. Tens of thousands of houses which were long ago condemned as unfit for human habitation were still occupied, and new slums were being created by the deterioration of existing property through neglect.

Lord WOOLTON, Lord President of the Council, said the whole Cabinet was determined, second only to the call for defence, to do everything to encourage local authorities and the building industry in their efforts to meet the housing needs of the country. He would be glad to see increasingly large numbers of dwellings built for elderly people.

Pneumoconiosis and Byssinosis Benefit Scheme

In accordance with the Pneumoconiosis and Byssinosis Benefit Act, 1951,[1] a benefit scheme (S.I. 1952, no. 373) is to come into force on March 10. Under this scheme benefit will be paid to, or in respect of, persons who are totally disabled or have died after Dec. 31, 1949, from pneumoconiosis or byssinosis, and who can claim neither workmen's compensation nor benefit under the National Insurance (Industrial Injuries) Act, 1946. A totally disabled person is to receive a weekly allowance of 40s., which may be increased in certain circumstances. In cases of death dependants are to receive up to £300.

QUESTION TIME

Prescription Charge

Mr. ARTHUR BLENKINSOP asked the Minister of Health whether he would make an exception to his 1s. charge for N.H.S. prescriptions which cost less than that sum.—Mr. H. F. C. CROOKSHANK replied: It is proposed that when the prescription charge is in operation, items the *retail cost* of which is less than 1s., and which are not supplied against a prescription form, would be purchased over the counter in the ordinary way, and not under the National Health Service.

Grants for Spectacles and Dentures

In reply to a question Mr. OSBERT PEAKE, Minister of National Insurance, said that up to the end of January, 1952, assistance grants for dentures and spectacles amounted to £54,160 and £88,723 respectively.

Dental Services

Replying to Mr. BLENKINSOP, Mr. CROOKSHANK said that during the *nine months* ended Dec. 31, 1951, some 9,100,000 teeth were extracted, apart from those in emergency for which no data were available; 7,600,000 teeth were filled, and 970,000 sets of upper and lower dentures were supplied.

Hearing-aids

In answer to a question Mr. CROOKSHANK said that about 4000 applicants were waiting for bone-conduction hearing-aids. Clinical trials of an experimental aid were in progress.

Replying to a further question suggesting that he should exempt from payment for hearing-aids people who had already been examined and placed on the waiting-list, Mr. Crookshank said there were about 100,000 [illegible] applications and he could not undertake to exempt so large a *number*.

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[1] Silberstein, F., Molnar, K., Engel, P. *Klin. Wschr.* 1933, 12, 1694.

[1] See *Lancet*, 1951, ii, 985.

Surgical Appliances

Replying to a question Mr. CROOKSHANK said there was no intention to introduce a charge for artificial limbs, for most surgical aids needed by the seriously disabled, or for any appliances supplied to patients who were resident in hospital rehabilitation centres.

In answer to a further question Mr. CROOKSHANK stated that the appliances supplied to patients through the hospitals in England and Wales during the 12 months ended Dec. 21, 1951, could be grouped under the following headings:

Appliance	Number supplied in 12 months	Cost
		£
New surgical footwear..	46,465	395,000
Appliances for lower limbs	28,280	156,000
Trusses	19,085	35,000
Abdominal appliances	107,282	375,000
Suprapubic and kindred appliances ..	15,570	55,000
Appliances for upper limbs	3593	12,500
Spinal supports	58,656	410,000
Head and neck appliances	11,732	58,000
Elastic hosieries	35,520	80,000
Wigs	9756	125,000
Prostheses (artificial breasts, ears, eyes, noses, &c.)	11,715	29,000
Artificial arms	1937	51,500
Artificial legs	11,383	330,000
Artificial arm appliances	4058	15,000
Artificial eyes	7682	12,000
Invalid chairs and tricycles	10,108	685,073

Neglect and Ill-treatment of Children

In reply to a question Sir DAVID MAXWELL FYFE, the Home Secretary, said that the persons convicted of neglecting or ill-treating children in the years 1946–50 numbered 1068, 1045, 1040, 907, and 974, and in the first nine months of 1951, 775.

Births, Marriages, and Deaths

BIRTHS

CLAPHAM.—On Feb. 26, in London, the wife of Dr. John Clapham, Colonial Medical Service, Sarawak—a daughter.

ELDER.—On Feb. 23, at Little Hadham, Herts, the wife of Dr. Peter McA. Elder—a son.

EMBLETON.—On Feb. 23, the wife of Dr. John Embleton, of Wokingham—a son.

HESLING.—On Feb. 23, at Fulwood, Preston, the wife of Dr. Gordon Hesling—a daughter.

JONES.—On Feb. 20, in Liverpool, Dr. Jean Jones (née Beattie), wife of Dr. W. J. Jones—a son.

PAVILLARD.—On Feb. 27, at Singapore, the wife of Dr. Stanley S. Pavillard—a daughter.

RIDDELL.—On Feb. 28, in London, the wife of Dr. R. W. Riddell—a son.

ROBERTS.—On Feb. 14, in London, the wife of Dr. C. G. Roberts—a daughter.

ROBINSON.—On Feb. 18, at Canterbury, the wife of Dr. B. H. D. Robinson—a son.

SAMUEL.—On Feb. 20, in Johannesburg, the wife of Mr. Eric Samuel, F.R.C.S.—a son.

WILLIAMS.—On Feb. 22, in London, the wife of Dr. Eirian Williams—a son.

MARRIAGES

MATTHEWS—DENDY.—On Feb. 23, in London, Michael Bernard Matthews, M.B., to Edith Mary Dendy.

RYAN—FARMER.—On Feb. 23, in Bristol, Jeremiah Robert Ryan, M.B., to Pamela Mary Farmer, M.B.

DEATHS

BULL.—On Feb. 29, at Bedford, George Coulson Bull, M.B. Lond., F.R.C.S., aged 94.

CORMAC.—On Feb. 21, at Macclesfield, Harry Dove Cormac, M.S. Madras, D.P.M.

GREEN.—On Feb. 25, in London, Frederick James Green, M.C., M.D. Camb., aged 83.

PEARSON.—On Feb. 25, at Leicester, Dudley Garencieres Pearson, B.A., M.B. Camb.

POWER.—On Feb. 28, in London, Michael Patrick Power, O.B.E., M.C., L.R.C.P.E., late colonel, R.A.M.C.

SHAW.—On Feb. 24, Raymond Henry Shaw, M.S., of London, late of Great Yarmouth, aged 85.

SKEVINGTON.—On Feb. 29, at Windsor, Sir Joseph Oliver Skevington, K.C.V.O., F.R.C.S.

WHITE.—On Feb. 24, at Bishop's Stortford, John Arthur Temple White, O.B.E., M.R.C.S., aged 85.

Obituary

RICHARD HARMAN LUCE

K.C.M.G., C.B., M.A., M.B. Camb., F.R.C.S., F.S.A.

Major-General Sir Richard Luce, who died on Feb. 22 at his home in Romsey, was for many years senior surgeon to the Derbyshire Royal Infirmary.

Born in 1867, the son of Colonel C. R. Luce, D.L., he was educated at Clifton College and at Christ's College, Cambridge, where he obtained first-class honours in the natural sciences tripos. In 1893 he qualified from Guy's Hospital, and he held house-appointments there before he took the F.R.C.S. in 1894. After serving as house-surgeon in the York County Hospital he settled in general practice in Derby in 1895. There he was soon appointed surgeon to the Derbyshire Royal Infirmary, and he made a success of both general practice and consulting surgery. Originally a surgeon in the Volunteers, he was prominent in the formation of the Territorial Force in the North Midlands in 1909. He served throughout the 1914–18 war with distinction, being invested with the C.B. and the C.M.G., and after rising to the position of director of medical services of the Egyptian Expeditionary Force he was promoted K.C.M.G. in 1919.

On his return to Derby he gave all his time to consulting surgery, and he was appointed surgeon to the Children's Hospital as well as to the Royal Infirmary. In 1924, when he was due to retire from his hospital appointments in two years' time, he accepted nomination as Conservative candidate for Parliament. His election to represent the borough in which he had worked for so long was the result of votes cast on personal rather than political grounds. When he retired to Romsey he was elected to the Hampshire County Council, and he was mayor of Romsey from 1935 to 1937. In these years he devoted much of his time to archæology and published several papers on the history of Romsey and its Abbey. He also enjoyed music and sketching, and his interests touched life at many points.

A colleague writes: "Luce first started to practise surgery in the 'nineties, when general practitioners were learning to diagnose appendicitis in the early stages and to realise that immediate operation was the best treatment, and he carried out many operations in private houses, using his portable operating-table. For the first ten years of his practice he relied upon horse transport, using a bicycle for emergencies, but about 1906 he changed to a motor-car. His was a busy life, but he kept good time, was full of energy, and came promptly to the right decision, so that he was trusted by doctors and patients alike. A man of outstanding personality and charm, he is still remembered by the older generation in Derby, every one of whom has kindly thoughts of him, and his reputation lives with those who never met him."

Lady Luce, one son, and three daughters are living. His second son died in India.

ANDREW GORDON CURRIE NEILL

M.B. Edin., F.R.C.S.E.

Mr. Gordon Neill, assistant surgeon to the East Cumberland hospital group, died on Feb. 21 at the age of 34.

He did well at Sedbergh and at Edinburgh University, where he graduated M.B. with honours in 1941. After serving as house-surgeon and as house-physician at the Cumberland Infirmary, Carlisle, he was appointed resident surgical officer to Hull Royal Infirmary. In 1943 he took the F.R.C.S.E. and returned as R.S.O. to the Cumberland Infirmary, to which he was appointed honorary assistant surgeon in 1947.

A colleague writes: "Early in his professional career Neill came under the influence of Mr. J. N. J. Hartley, under whose guidance he became at an unusually early age a surgeon of wide experience, mature judgment, and exceptional technical achievement. A modest manner cloaked an inner strength which gave his patients confidence, so that they became his friends. He accomplished a vast amount of work yet never seemed to be hurried.

He had a serene temperament, a prodigious memory, and a genuine interest in the welfare of his patients for each of whom, no matter how weary he must have been, he had a kind word. He abhorred the idea of destructive surgery and turned his attention more and more to plastic surgery, at which he soon became adept.

"He was well-read and had an interest in many subjects, not least in history and the classics. To an extraordinary degree he had developed the faculty of reaching the core of a problem through a mass of detail. This enabled him to reach a reasoned decision in his work and helped to make him an admirable secretary to the medical board and later to the medical advisory committee of his hospital. He held firm beliefs and opinions but saw the other man's point of view clearly enough never to irritate nor to give offence in a discussion. The chief memory he leaves is one of quiet equanimity and unobtrusive hard work by which he achieved his aim—to become an 'operating physician.' He leaves a widow and two baby daughters."

The list issued by the Foreign Office of British subjects killed during the recent riots in Cairo includes the name of Surgeon-Commander WILLIAM SLOAN MILLER, R.N., who graduated M.B. from the University of Glasgow in 1936.

Appointments

TRYTHALL, D. A. H., M.D. Lond., M.R.C.P., D.C.H.: asst. medical registrar, The Hospital for Sick Children, Great Ormond Street, London.

Manchester Regional Hospital Board:

BEVIS, D. C. A., M.B. Manc., M.R.C.O.G.: consultant obstetrician/gynæcologist, Park Hospital, Davyhulme.

FREETH, H. D., M.D. Lond., M.R.C.O.G.: consultant obstetrician/gynæcologist, Crewe Hospital Centre.

HUTTON, E. M., M.B. Dubl.: asst. psychiatrist and deputy medical superintendent (S.H.M.O.), Calderstones Hospital.

MEHLMANN, SAMUEL, MED. DIP. Lwow: asst. anæsthetist (S.H.M.O.), Rochdale Hospitals.

OELBAUM, M. H., M.D. Manc., M.R.C.P.: consultant general physician, Crumpsall Hospital, Manchester.

PARKER, C. S., M.D. Manc., D.P.M.: consultant psychiatrist, Preston and Chorley Hospital Centre and Whittingham Hospital.

RUSHWORTH, C. D., M.R.C.S.: tuberculosis physician, Wigan and Leigh hospital areas.

SMITH, F. W., M.B. Manc., M.R.C.P.: consultant general physician, Macclesfield Hospital Centre.

Oxford Regional Hospital Board:

ANDERSON, H. A., L.R.C.P.E.: deputy physician-superintendent and asst. psychiatrist, Pewsey Hospital, Pewsey, Wiltshire.

HARRIES, R. W., M.R.C.S.: asst. pathologist (S.H.M.O.), High Wycombe area.

WATT, D. C., M.D. Glasg., D.P.M.: consultant psychiatrist to general and mental hospitals, Aylesbury area.

YOUNG, R. V., B.M. Oxfd: asst. pathologist (S.H.M.O.), Banbury area.

Sheffield Regional Hospital Board:

HANNAH, L. G. W. J., M.B. Lond.: asst. psychiatrist to Rauceby Mental Hospital, near Sleaford, Lincs.

MOORE, G. L., L.R.C.P.I.: asst. chest physician, Chest Clinic, Leicester.

VALENTINE, A. A., M.B. St. And., D.P.M.: consultant psychiatrist, Glenfrith Hospital, Leicester.

South Western Regional Hospital Board:

FORBES, H. A. W., B.M. Oxfd, M.R.C.P.: consultant physician, Plymouth clinical area.

LYNCH, G. A. C., M.D. Lpool, D.P.H.: consultant pathologist, Plymouth clinical area.

VELLACOTT, H. D. S., M.B. Camb., F.R.C.S.: consultant surgeon, Plymouth clinical area.

Welsh Regional Hospital Board:

JONES, H. O., M.S. Lond., F.R.C.S.: consultant surgeon to United Cardiff Hospitals and Welsh R.H.B.

MORGAN, D. B., M.D. Lond.: asst. chest physician (S.H.M.O.), Glantawe H.M.C.

THOMAS, J. H., M.R.C.P. Lond., D.C.H.: asst. chest physician (S.H.M.O.), Glantawe H.M.C.

WILSON, J. N., CH.M. Birm., F.R.C.S.: part-time consultant orthopædic and traumatic surgeon, United Cardiff Hospitals and Welsh R.H.B.

The Terms and Conditions of Service of Hospital Medical and Dental Staff apply to all N.H.S. hospital posts we advertise, unless otherwise stated. Canvassing disqualifies, but candidates may normally visit the hospital by appointment.

Notes and News

NICOTINIC ACID ISOMER DERIVATIVES IN TUBERCULOSIS

OUR annotation last week quoted a statement made to press by Dr. Geoffrey Rake, director of the Squibb Instit for Medical Research. In a letter to members of the medi profession in the United States, Dr. Rake writes: "Un circumstances beyond our control news of a new antituberculo drug has found its way into the lay press before completi of clinical studies, which are being energetically pressed, a adequate scientific publication. This drug, isonicotinic a hydrazide, named 'Nydrazid' by Squibb, is one of ma thousands of compounds screened for antituberculous activ in the Squibb Laboratories in recent years. It has been clinical trial for no more than a matter of months. T clinical workers believe that the drug holds promise but th will not be in a position to publish until April, at which ti papers on the pharmacology of the drug, on laboratory wo and on the clinical findings will appear in the *Americ Review of Tuberculosis.* Nydrazid will be made available the medical profession as promptly as possible after the fili of adequate clinical data with the U.S. Food and Dr Administration, and if the drug is released by that agenc Meanwhile we wish to assure you that we regret the prematu announcement of nydrazid to the public as much as a members of the profession which we serve." Messrs. Roc Products Ltd., who are preparing the same drug under t name of 'Rimifon,' inform us that the Roche organisati likewise intended to make their first announcement in Apr

GUY'S HOSPITAL DENTAL SCHOOL

THE annual clinical meeting of Guy's Hospital Dent School was held on March 1. The meeting opened with grimly fascinating lecture by Dr. Keith Simpson on Murde it was illustrated by a series of suitably gruesome lante slides and enlivened by Dr. Simpson's pithy comments some of the more unusual cases in which he has been co cerned. Although few of us will ever come across so ma bodies found dead in suspicious circumstances as has D Simpson, his lecture served to emphasise the value of accura observation and the importance of apparently trivial detail

It is only possible to mention a few of the many demon trations. Mr. S. H. Wass, with Dr. T. A. B. Harris anæsthetist, performed an operation for the removal of neur fibromatous masses from the alveoli of a patient who h suffered for many years from von Recklinghausen's diseas and who presented an almost textbook picture of th condition. Mr. Wass said he did not favour the routine u of hypotensive drugs in oral surgery, and he confines their u to those under 50; he relies on tilting the table to minimi hæmorrhage during the operation.

The department of bacteriology showed some of the resul of an investigation, which is still proceeding, into the effica of various antiseptics. Of all the chemicals tested so fa iodine has proved the best. It is not the ideal antiseptic, b a 3·5% solution in alcohol will sterilise the buccal muco membrane instantaneously, whilst a slightly less irrita preparation made by the addition of glycerin to this mixtu is almost as effective. Absolute alcohol and dilutions of le than 50% are almost useless, and even the 70% solution is le effective than has been supposed. It was found that instr ments need 30 min. immersion in 5% 'Dettol' for sterilisatio and that the antiseptic power of aqueous solutions of dett deteriorates with age.

Research which may well lead to a better understandi of some of the problems of dental caries is being carried o by Mr. M. V. Stack in the department of dental medicin Since the fairly general acceptance of the view that cari begins by a process of proteolysis rather than by one decalcification, the organic content of enamel has assumed much greater significance than formerly. The non-wate soluble protein present is keratin, but there is also a wate soluble protein whose nature is being investigated by pap chromatography. A point of interest is the use of a ne decalcifying agent, ethylene diamine tetracetic acid, whic will decalcify bone or enamel at a pH of 7·5.

Dr. L. Forman, physician to the skin department, show several cases of dental interest, including two of oral pe phigus. This distressing, but fortunately rare, conditio can be controlled successfully by either A.C.T.H. (150 mg. p day) or cortisone (300 mg. per day). There is no question of from this treatment, and both the patients showed the ..cteristic changes—hirsuties, " moonface," &c.—caused rolonged administration of these drugs, but the treatment nsidered amply justified by the otherwise bad prognosis is disease.

he staff of the Dental School are to be congratulated on ng arranged yet another clinical meeting that has main- ed the high standard set by its predecessors.

BRITISH RHEUMATIC ASSOCIATION

HIS association is conducting a campaign to increase ities for the treatment of rheumatic conditions, especially those patients who live far from a hospital. A Ministry Health circular in 1949 recommended the cancellation of tracts between regional hospital boards and those voluntary ies which run mobile physiotherapy units and village ics. The association pointed out how patients in remote s would suffer, and the enforcement of the directive has o been postponed. A deputation led by the association Ministry officials to plead that " the voluntary organisa- s should be recognised as an integral part of the scheme." otiations are continuing.

he fourth annual report of the association also says that gadget " committee is studying all the little devices ch can make life easier for the disabled patient—retrieving ks, zip-fastening boots, and so on. A handbook about n will be issued jointly with the Central Council for the e of Cripples. The association's book already published alled *Rheumatism and You*; it is designed to encourage erers by showing them how much they can do to help mselves and to combat the apathy which often overcomes m. The book is distributed by Simpkin Marshall at 5*s.*, may be ordered from booksellers or direct from the ociation at 5, Tite Street, London, S.W.3.

PEOPLE, NURSES, AND THE MENTAL SERVICES

IENTAL nursing has always been hard, and used to be couraging as well. Now, with the vigorous growth of v methods of treatment, it is becoming a worthy and acting career for capable people. Unfortunately its old popularity still persists, partly no doubt because few nurses ve the opportunity of seeing the work done in a mental spital unless they join the staff. Recruits are relatively rce, and shortage of staff not only keeps the work hard t also fosters a high rate of wastage. On Feb. 27, 28, d 29 a conference, arranged by the Royal College of Nursing, t " to consider means of promoting mental health and ffing the mental health services, through sound adminis- tion and wise education."

That the work has changed, and is changing, was generally reed. Sir PERCY BARTER noted that in 1939 there were ,900 admissions to mental hospitals in England and Wales, d 18,700 discharges, whereas in 1949 there were 51,400 missions and 39,900 discharges, which represents a rise in discharge-rate of 10%; but the most startling assessment this change came from Dr. THOMAS BEATON, physician- perintendent of St. James's Hospital, Portsmouth, who id that 26 years ago the average stay of patients in this spital was 10 years, whereas it is now 4–6 weeks. People ust be taught, Dr. Beaton insisted, what the mental hospitals ; and this can be achieved by letting them come into e hospitals to see for themselves, and by talking to them various social groups such as societies, rotary clubs, church cial clubs, and the like. We can also teach them something out the causes of mental ill health. Life is more secure some ways than it used to be, but it is also more hedged , and makes greater demands. Thus, at one time, inability read and write was not evidence of failure to develop tellectually: now it is. At one time, too, children had a od many outlets for physical exuberance, but now a boy as only to climb a lamp-post and he is up before the " beak." They used to run away to sea, but they can't now, owing all the planning that goes on."

Dr. DENIS LEIGH, with proper Maudsley caution, warned gainst indiscriminate teaching of the public until we knew etter what we wanted to teach. We would all like more nd better psychiatrists, child psychologists, mental defective ervices, and hospitals, and more education of the public in ental welfare; but is our psychological knowledge sufficiently r advanced to train either the public or the psychiatrists? hrough the centuries, he finds, the recovery-rate of mentally l people seems to have stood roughly constant at about wo-thirds of the admission-rate. Effective psychotherapy ust either speed up the recovery-rate, increase the proportion recovering, prevent recurrence, or reduce the tensions in the patient; and evidence that our present forms of psychotherapy can do any of these things is, he thinks, scanty. Our primary needs are for research, experiment, and restraint in our claims.

Dr. ADAM MILNE had solved along his own lines the practical problem of attracting enough nurses to look after the mentally sick. Kingseat Mental Hospital, Aberdeen, has had a full staff for 18 months, and even has a waiting-list. The nurses there learn that they have an aim: to get people well. They think of the hospital as theirs, and are encouraged to realise that they are not working for their salaries, or their chiefs, but for the sake of a job that is worth doing. Nurses who cannot fit in with this idea are not kept on. When Dr. Milne hears complaints about the " poor material " entering mental nursing, he is inclined to wonder whether there are faults in the superintendent and the matron. Too many of these officers, he thinks, have grown up into the job, and no-one has ever considered whether they are capable of building the job up into something better. It is a problem in morale. He and his matron treat their nurses as colleagues. Even the junior students are encouraged to add their observations to the case-notes.

This is a personal solution: not everyone, perhaps, could achieve it, though surely all should try. In the course of discussion the suggestion was mooted that every nurse, *during her general training*, should do three months' work in a mental hospital. It was objected by a mental hospital matron that this would not give her time to gain any insight into mental illness, and that in a small establishment it would be extremely unsettling to patients to have new nurses coming and going every three months. The second of these objections certainly deserves serious consideration, but it is hard to see the force of the first. Three months is equal in length to a term-and-a-half at a university, and should certainly allow a nurse, working all day in the wards, to form more than a passing impression of her subject. Compared with the half-dozen or so lectures and demonstrations usually accorded to medical students in this important subject, it is a very handsome allowance indeed. It would in any case give nurses a chance to find out whether this type of work attracted them as a future career.

University of Cambridge

On Feb. 23 the following degrees were conferred:

M.Chir.—*G. M. Lunn.

M.B., B.Chir.—C. McC. Campbell, I. H. Kerr, *Katharine C. Paterson, *R. F. Pearson.

* By proxy.

Royal College of Surgeons of England

On Friday, April 4, at 5 P.M., at the college, Lincoln's Inn Fields, W.C.2, Sir James Learmonth will deliver the Lister oration. The title of his lecture is After Fifty-six Years.

Association of Sea and Air Port Health Authorities of the British Isles

The annual meeting of the association will be held at Rochester from June 11 to 13. The speakers will include Dr. M. T. Morgan, Dr. R. H. Barrett, Dr. J. O. Murray, Dr. J. S. Jackson, Surgeon Captain S. G. Rainsford, and Dr. Thomas Peirson.

Medical Officer to the L.C.C.

On March 4 the London County Council appointed Dr. J. A. Scott, the present deputy medical officer of health, to be the council's medical officer of health and school medical officer in succession to Sir Allen Daley, who has retired. The salary of the post is £3500 a year. Ten applications were received, and four candidates were interviewed.

Dr. Scott, who is 51 years old, was born in Liverpool and educated at Liverpool Institute and Liverpool University. After holding appointments as R.M.O. at Liverpool hospitals, he joined the staff of Surrey County Council as assistant M.O.H. in 1927. Thereafter he was successively M.O.H. for Shipley, Barnsley, and Fulham. For his services to civil defence in Fulham he was appointed O.B.E. in 1941. Dr. Scott entered the L.C.C.'s service as a principal medical officer in 1945, and he was placed in charge of the central planning division of the public-health department, where he was closely associated with post-war developments. After the passing of the National Health Service Act in 1946, he was directly concerned with the reorganisation of the department, and the arrangements necessary to enable the council's new functions to be carried out. In 1948 he was promoted to be deputy medical officer of health. He was awarded a Rockefeller travelling fellowship in 1949, and he spent two months in America studying public-health teaching and practice. He is a member of the Central Midwives Board.

National Formulary, 1952

The *National Formulary, 1952,* will replace the 1949 formulary on June 1. National Health Service chemist-contractors will receive copies from executive councils soon after publication.

Congress of Dietetics

The first international Congress of Dietetics is to be held at Amsterdam from July 7 to 11 under the presidency of Prof. B. C. P. Jansen. Further particulars may be had from the educational bureau of the Nutrition Council, 42, Koninginnegracht, The Hague, Holland.

Seaweed Symposium

An International Seaweed Symposium, sponsored by the Institute of Seaweed Research, Inveresk, Midlothian, is to be held in Edinburgh from July 14 to 17. Further particulars may be had from Mr. T. W. Summers, secretary to the organising committee, at the institute.

British Standards

A standard (B.S. 1823 : 1952) has been issued for small stainless-steel holloware utensils for use in hospitals. Specifications are given for instrument trays, kidney dishes, wash bowls, lotion bowls, and gallipots. Copies of this *standard (2s.) may be had from the British Standards Institution, Sales Department, 24, Victoria Street, London, S.W.1.*

Closed-shop Dispute

Dr. John Dryden, Dr. John Young, Dr. Euphemia Guild, Dr. Frances Carr, and Dr. Joyce Vasey, who have been appointed to posts under the education authority of Durham County Council, will not at present take up their appointments, because the "closed-shop" dispute between the British Medical Association and the council is still unsettled. A member of the education committee in a statement to the press (*Manchester Guardian*, March 1) said:

> "A conflict with the Ministry of Health appears imminent. All would have been well had the council accepted the recommendation of the Emergency Committee to exempt doctors from the rule that applications [illegible] must go through a union or professional [illegible] A. would then have lifted its ban and th [illegible] appointments. Instead, the council se [illegible] back to the Emergency Committee.
>
> "The Ministry has been considerate over the fact that we have not been able to make more frequent medical inspections at schools. This was because of the general shortage of medical officers. Now, however, the council appears to be deliberately keeping the dispute going, which means in effect it is not fulfilling its obligations in the school health service."

Anglo-French Exchange Bursaries

The French Embassy in London has arranged for an exchange of short-term grants between the Institut National d'Hygiène in Paris and the Ciba Foundation in London, to enable young British and French doctors to visit each others' countries and study special techniques. The grants, which will be of at least £50 a month tax-free, will be awarded for periods of two to six months to doctors who wish to obtain clinical experience, but they can also be awarded for medical research. The British selection board is composed as follows: Prof. Alexander Haddow, Prof. John McMichael, the British Council (Dr. Margaret Suttill), the British Postgraduate Medical Federation (Dr. C. F. Hamilton-Turner), the Medical Research Council (Dr. F. J. C. Herrald), joint secretaries Miss A. M. Vidal-Hall (French Embassy) and Dr. G. E. W. Wolstenholme (Ciba Foundation). Applications for the 1952 bursaries should be sent before March 31 to Dr. Wolstenholme, director, Ciba Foundation, 41, Portland Place, London, W.1.

EMERGENCY BED SERVICE.—In the week ended last Monday applications for general acute cases numbered 1138. The proportion admitted was 87·5%.

CORRIGENDUM: *Familial Intestinal Polyposis.*—In this article by Dr. H. H. Wolff last week (p. 446) fig. 1 was printed the wrong way up.

The *Journal of Clinical Endocrinology* has been renamed the *Journal of Clinical Endocrinology and Metabolism.*

The British Council has coöperated with the British Medical Association in arranging a visit by Prof. F. A. R. Stammers to Bagdad, Cyprus, and Khartoum.

Messrs. Vitamins Ltd. offer a limited number of places to doctors who wish to view the Boat Race from their premises on March 29. Tickets may be had from Dept. B.R.1, Vitamins Ltd., Upper Mall, London, W.6.

Diary of the Week

MARCH 9 TO 15

Monday, 10th

MEDICAL SOCIETY OF LONDON, 11, Chandos Street, W.1
8.30 P.M. Dr. G. W. B. James, Dr. P. M. Tow: Therap Trauma of the Brain.

INSTITUTE OF NEUROLOGY, National Hospital, Queen Square, W
5 P.M. Prof. J. C. Eccles (Canberra): Physiological Respo of Chromatolysed Neurones.

INSTITUTE OF PSYCHIATRY, Maudsley Hospital, Denmark Hill, S
5.30 P.M. Dr. E. Stengel: Lecture-demonstration.

Tuesday, 11th

ROYAL COLLEGE OF PHYSICIANS, Pall Mall East, S.W.1
5 P.M. Prof. John McMichael: Dynamics of Heart-fail (First of two Oliver-Sharpey lectures.)

INSTITUTE OF DERMATOLOGY, St. John's Hospital, Lisle Str W.C.2
5.30 P.M. Dr. S. C. Gold: Contact Allergy.

WEST END HOSPITAL FOR NERVOUS DISEASES, 40, Maryleb Lane, W.1
5.30 P.M. Dr. T. Rowland Hill: Neurological demonstratio

CHELSEA CLINICAL SOCIETY
8.30 P.M. (South Kensington Hotel, 41, Queen's Gate Terra S.W.7.) Dr. R. E. Smith: The School Doctor Looks Forwa *and Backwards.*

MANCHESTER MEDICAL SOCIETY
4.30 P.M. (University of Manchester.) *Sections of Surgery a Medicine.* Dr. F. Avery Jones: Treatment of Hæm temesis.

Wednesday, 12th

UNIVERSITY COLLEGE, Gower Street, W.C.1
5.30 P.M. Prof. R. B. Cattell (Illinois): Recent Quantitati Research on Personality and the Culture Pattern.

INSTITUTE OF DERMATOLOGY
5.30 P.M. Dr. I. W. Whimster: Origin of Epithelial Neoplas in the Skin.

LONDON COUNTY MEDICAL SOCIETY, St. James' Hospital, Balha S.W.12
3 P.M. Clinical meeting.

MANCHESTER MEDICAL SOCIETY
4.30 P.M. *Section of Pathology.* Dr. J. E. Kench: Porphyri in Health and Disease.

Thursday, 13th

ROYAL COLLEGE OF PHYSICIANS
5 P.M. Professor McMichael: Dynamics of Heart-failu (Second of two Oliver-Sharpey lectures.)

ROYAL COLLEGE OF SURGEONS, Lincoln's Inn Fields, W.C.2
5 P.M. Prof. V. W. Dix: Ureteric Calculus. (Hunteri lecture.)

BRITISH POSTGRADUATE MEDICAL FEDERATION
5.30 P.M. (London School of Hygiene, Keppel Street, W.C. Sir Cyril Burt, D.SC.: The Psychology of Personality.

UNIVERSITY COLLEGE
5 P.M. Prof. Wilson Smith, F.R.S.: Structural and Function Plasticity of Influenza Viruses. (Sydney Ringer lectur

INSTITUTE OF CHILD HEALTH, The Hospital for Sick Childr Great Ormond Street, W.C.1
5 P.M. Mr. H. S. Sharp: The Ear, Nose, and Throat.

INSTITUTE OF DERMATOLOGY
5.30 P.M. Dr. H. Haber: Histopathology of Foreign-body a Specific Granulomas.

ROYAL ARMY MEDICAL COLLEGE, Millbank, S.W.1
5 P.M. Dr. D. Evan Bedford: Common Difficulties in t Diagnosis of Heart-disease.

ST. GEORGE'S HOSPITAL MEDICAL SCHOOL, Hyde Park Corner, S.W.
4.30 P.M. Dr. Desmond Curran: Psychiatry lecture-demonstr tion.

ALFRED ADLER MEDICAL SOCIETY
8 P.M. (11, Chandos Street, W.1.) Dr. E. K. Lederman Relationship of Body and Mind.

MANCHESTER MEDICAL SOCIETY
8.15 P.M. *Section of Anæsthetics.* Dr. W. B. Bacon, Dr. C. Sykes: *Control of Bleeding During Surgical Operation*

UNIVERSITY OF ST. ANDREWS
5 P.M. (Medical School, Small's Wynd, Dundee.) Sir He Dale, O.M., F.R.S.: Transmission of Effects from Nerv endings.

MEDICAL SOCIETY FOR THE CARE OF THE ELDERLY
11.30 A.M. (B.M.A. House, Tavistock Square, W.C.1.) Dr. J. Scott, Dr. E. B. Brooke, Dr. Barbara Morton: Coördinat Medical Care of the Elderly.

Friday, 14th

INSTITUTE OF DERMATOLOGY
5.30 P.M. Dr. S. C. Gold: Contact Eczema.

INSTITUTE OF DISEASES OF THE CHEST AND INSTITUTE OF CARDIOLO
5.30 P.M. (London School of Hygiene.) Mr. R. C. Broc Surgical Treatment of Mitral Stenosis.

MEDICAL SOCIETY FOR THE C[illegible]
10 A.M. (Langthorne Hosp [illegible] Dr. J. A Herd: Psychiatric [illegible] Hospit Dr. P. J. Sonnek: [illegible] the Ag Dr. Trevor Howell: Medical Care of Old People. (Fi

AN INTERPRETATION OF STATISTICAL TRENDS IN TUBERCULOSIS*

V. H. Springett
M.D. Lond.

PROPHIT SCHOLAR OF THE ROYAL COLLEGE OF PHYSICIANS OF LONDON; CLINICAL ASSISTANT, GREENWICH CHEST CLINIC

In his suggestions for lecturers Dr. Milroy laid stress on the need for accurate study of the geography and chronology of diseases. It is apparent that here he had in mind acute epidemic diseases, but I propose in these Milroy lectures to develop this approach in studying tuberculosis mortality.

My original intention was to gather together tuberculosis mortality-rates for age-groups of each sex for a number of countries where these details had been recorded for at least fifty years. My object was to determine which features of the rates were common to all countries at all times, and therefore presumably due to unchanging fundamental factors. Other special features would be shown only by some countries at certain times, and these might reasonably be associated with local environmental differences. I have elsewhere placed on record these collected data (Springett 1950) and I propose now to give detailed analyses for this country only, referring in a general way to the rates for other countries to illustrate special points of similarity or difference.

Tuberculosis Mortality-rates by Sex

Fig. 1 shows the tuberculosis mortality-rates for England and Wales in age-groups of each sex for 1949. For the first few years of life the rates for males exceed those for females. In each sex there is then a fall to a low level during the early school years. Then for the age-group 10–14 there is an increase in rate which is much greater for females than for males, and this excess of female rates over male rates continues to the age of 20–24. Over that age the male rates are the greater, with rates from three to four times those for females in the older age-groups.

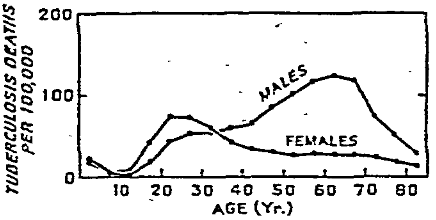

Fig. 1—Mortality from all forms of tuberculosis in England and Wales in 1949.

Certain features of these curves have been remarkably constant. There has always been a fall from the rate for the first 5 years of life to that for the second quinquennium. The high rates of infancy have always been greater in the male, but this fact should not perhaps eceive undue emphasis in this context, since it is true of many causes of death at this age. For all causes combined he male rate exceeds the female by 20%, and the higher uberculosis mortality is presumably only one mani-station of this generally greater frailty of the male. The rise in mortality after 10 years of age, on the other and, as is well known, is greater in females, and this is emarkable in that I have been able to find no other ause of death common to both sexes for which the male rates are so strikingly and constantly in excess the male rates at this age. I would emphasise, however, that the rates do increase after the age of 10 years r each sex.

After this rise at about the time of puberty the rates ve always reached a maximum at some time during adult life, either early or late, with finally a fall to lower rates in old age. That is the general pattern—high in infancy, low in early childhood, with a rise to a peak in adult life, and a final fall as a constant finding at all times in most communities. But within this general pattern there have been considerable changes of emphasis, as may be seen for the males of England and Wales in fig. 2, which shows the tuberculosis mortality-rates for males in decennia at 20-year intervals between 1851–60 and 1931–40; the rates for the age-group 0–4 years are omitted. It is obvious that, during this period, mortality has fallen considerably in every age-group, but in some more than in others. The fall in rate was first apparent in young adult life at a time when little or no improvement was occurring in the rates for older age-groups, and it was only after the rate for young adults had been falling for a considerable period that the improvement began in older age-groups. One result of this was that, whereas in 1851–60 the highest rate of tuberculosis mortality was at 25–34 years, in 1871–80 it was at 35–44, and from that time until 1931–40 it was at 45–54. As shown in fig. 1 the highest rate is now at 55–64 years. The present peak of mortality late in life is thus seen to be a culmination of a gradual process in which the maximum mortality has moved from young adult life through middle age to the older age-groups.

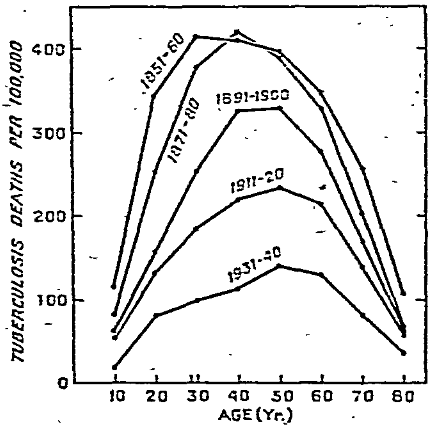

Fig. 2—Mean annual mortality in males from all forms of tuberculosis in England and Wales in decennial periods.

If now we consider the rates for females over the same period of time (fig. 3) we see that, as for males, the maximum occurred at 25–34 in 1851–60, though the decline in rate above this age was much more steep than in males. Again, there has been a great fall in rate in all age-groups. This was at first much greater in young adults than in older age-groups, so that there was a shift of the peak of the curve to an older age-group—35–44 in 1891–1900. After this the rates for young adult females were almost stationary for a considerable time, with the result that the highest rate of mortality now occurs at 15–24.

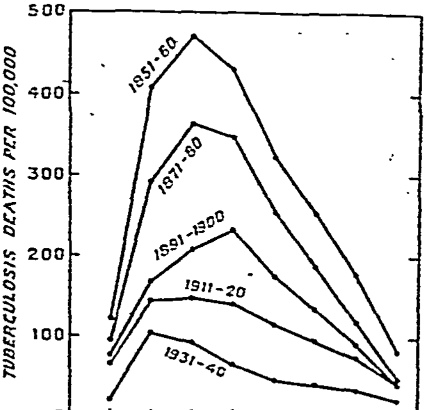

Fig. 3—Mean annual mortality in females from all forms of tuberculosis in England and Wales in decennial periods.

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* The Milroy lectures for 1952, delivered before the Royal College of Physicians on Feb. 12 and 14.

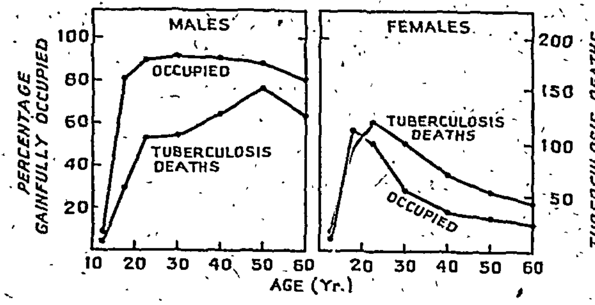

Fig. 4—Age-distribution of tuberculosis mortality in males and in females in relation to proportion gainfully occupied in 1931.

From this brief review of the rates in the last hundred years two points of special interest emerge and have been specially studied. In males the point of particular interest is the gradual shift of the peak from young adult life to an age about the end of working life, and it is this problem to which I propose to devote the remainder of this lecture, proceeding in the second lecture to the point of particular interest shown by the rates for females—namely, the almost complete arrest of the decline in young adults in the early years of this century. Finally, I propose to discuss possible reasons for the fall in rate in each sex.

Shift of Peak Mortality in Males

In studying the shift of the peak in males it is, I think, important to remember that the shift began *shortly after the middle of the last century, and that at* that time there was a similar but smaller shift of the peak for females.

Among the earlier papers on this subject of tuberculosis mortality in England and Wales were those of Brownlee, and in papers published in 1918 and 1920 he noted the great differences between the curves for males and females, with the gradual development of increasing excess in the male rates in the older age-groups. His observations on these facts were entirely accurate, but his development of a hypothesis that they were due to various types of disease affecting different age-groups, and due to different types of bacillus, would not now find support.

A further observation of Brownlee's is an early statement of what subsequent writers on this subject (including myself) have largely assumed, and that is the validity of these death-rates from tuberculosis. Brownlee regarded the rates as trustworthy because it seemed to him impossible that the constancy of the results of these analyses could possibly exist unless the basic rates were reasonably accurate. I can see no direct way of checking the accuracy of these rates, and I agree with Brownlee that their very regularity is fairly good evidence that they are a reasonably accurate reflection of what has been happening. However, let me admit at this stage that I have no reply to the criticism that the rates are so inaccurate as to nullify any detailed analysis. If anyone wishes to take up that position, then all the peculiarities of the rates to which I have referred can be attributed to their inaccuracies: there is then no point in further study or attempts at interpretation.

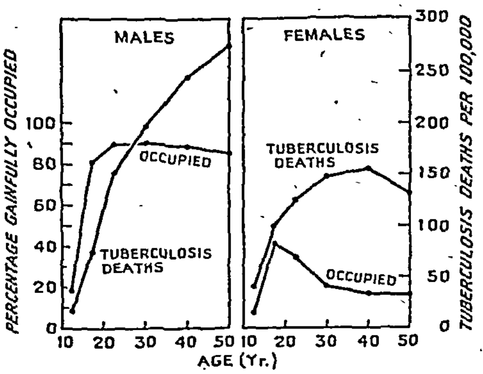

Fig. 5—Age-distribution of tuberculosis mortality in males and in females in relation to proportion gainfully occupied in 1901.

Hart and Wright (1939) relate the differing age-distribution of mortality in men and women to the different proportion of the sexes gainfully occupied. Using the data for 1931 they do show some similarity—fig. 4 is based on the charts and figures in their work—but if the comparison is made for an earlier period (fig. 5), the relationship disappears. The data are available only from 1901 but the percentage gainfully occupied is practically constant at each census, whereas the tuberculosis mortality distribution has shown steady changes over a long time.

Stocks (1949) has *attributed the present high rate in* older males to the fact that this group of men has borne the brunt of two wars and lost many of their fittest in the first. I have no doubt that these factors have made the rates higher than they would otherwise be, and account for the actual increase in rates that has taken place in recent years; but, as Stocks recognises, wartime influences cannot explain the steady shift of the peak of mortality, a shift which began in the last century and was then occurring also in women.

MEAN ANNUAL MORTALITY FROM TUBERCULOSIS (ALL FORMS) IN MALES IN ENGLAND AND WALES IN DECENNIAL PERIODS 1851–60 TO 1931–40 AND IN 1942–49

Period	Age-group (years)							
	5–	15–	25–	35–	45–	55–	65–	75–
1851–60 ..	116	344	416	412	396	348	257	106
61–70 ..	97	321	421	424	397	343	217	74
71–80 ..	83	254	378	420	393	328	202	65
81–90 ..	73	202	316	368	361	303	191	73
91–1900 ..	61	157	254	325	330	277	171	63
1901–10 ..	55	137	216	262	293	257	169	67
11–20 ..	55	132	184	220	234	214	139	58
21–30 ..	32	111	140	164	173	146	96	41
31–40 ..	18	81	99	113	139	129	81	36
42–49 ..	12	49	68	77	109	124	85	35

Dahlberg (1949), dealing with the rates experience in many countries in the early part of the 1930s, show that the rates for the United States, Italy, France, an Germany all reveal a considerable excess of male mortali in the older age-groups, whereas in Norway and Swede the rates for the two sexes are essentially similar—t female rates a little the greater in young adult life, t male rates a little the greater in old age. The rates f Finland were rather intermediate in type, because t male curve showed two peaks, at 20–24 and 60–64, wit low *point* at 40–44. The rates for Denmark also i interesting, especially as they are extremely low. I each sex there is a maximum in young adult life, t only a slight fall with increase of age.

In his discussion of these results, Dahlberg associa the differences with the greater degree of urbanisati in the larger countries. By separating the rates f Stockholm from rural areas of Sweden, and those o *Copenhagen from rural areas of Denmark*, he shows tha the rates for these capital cities tend to conform to the pattern of large urban countries like Great Brita whereas those of the rural areas of Sweden and Denma are similar to those for Norway, with comparati little difference between the sexes in the rates for ol age-groups. Dahlberg concludes that infection at place of work is the deciding factor, an explanati similar to that advanced by Hart and Wright (1939), which I have found unacceptable for this country because of inconsistencies when studied over a long period. However, I think Dahlberg's point that a great discrepancy in rates in older life is a feature of highly urbanised communities is valid, though I do not agree with his further explanation that contact at the place of work is responsible.

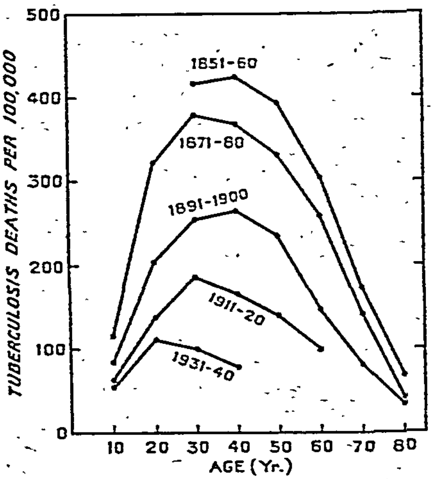

Fig. 6—Mortality from all forms of tuberculosis in male cohorts (England and Wales). Dates indicate the decennium in which the cohort was aged 25–34 years.

COHORTS

I have purposely left until last consideration of a group of papers based on a rather different approach. The most important of these is by Wade Hampton Frost (1939), who studied the tuberculosis mortality of groups of people born about the same time, rather than that of age-groups of people alive in a given calendar year or group of calendar years. The method had been used earlier for tuberculosis mortality by Andvord (1930), but Andvord's paper dealt only with the mortality of the first 30 years of life and had no direct bearing on the shift of the peak of mortality to later life. Frost dealt with the data for Massachusetts. I propose to discuss the method now in more detail, using the tuberculosis mortality of England and Wales.

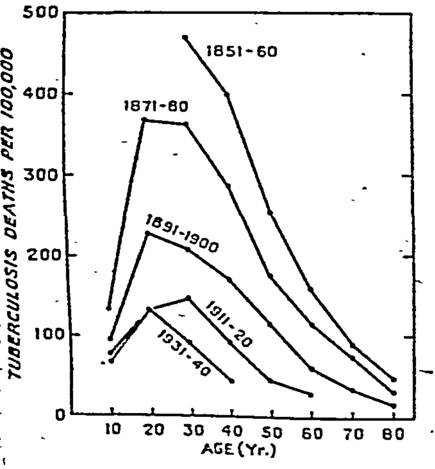

Fig. 7—Mortality from all forms of tuberculosis in female cohorts (England and Wales). Dates indicate the decennium in which the cohort was aged 25–34 years.

The accompanying table shows the method common to all these papers. It gives the mean annual tuberculosis mortality-rates per 100,000 living for males in 10-year age-groups of England and Wales for decennia in the past century. Reading along the rows of such a table, we have a record of the experience of the various age-groups in the decennium concerned; when plotted graphically, these figures give the curve of the age-distribution of mortality of which I have already shown examples. Reading down the columns of such a table, we have the experience of a given age-group in successive decennia, and this method, too, is reasonably familiar in the form of a graph showing the more or less regular decline of mortality over a period for a given age-group.

But there is a third way of reading the table and plotting the results—namely, diagonally from top left to bottom right as it is here set out. Provided that the time interval between the horizontal rows is the same as that between the vertical columns—in this case, 10 years for each—reading diagonally gives the tuberculosis mortality of the survivors of a group of people born about the same time. Such a group of similar birth-date Frost (1939) called a "cohort," and the distribution of tuberculosis mortality by age in successive cohorts is a matter of considerable interest.

Fig. 6 shows the tuberculosis mortality of a series of cohorts of males in England and Wales. The form of the curves is essentially similar throughout (the rates for infancy are omitted): it is low in childhood and then there is a peak in adult life, never at a greater age than 35–44. Even more interesting, there is no tendency for the peak to pass to an older age-group: indeed in the more recent cohorts the peak tends to occur in younger age-groups. This tendency is even more conspicuous in the females of England and Wales (fig. 7). Here the adult peak of mortality occurs regularly at 25–34, moving finally to the younger age-group 15–24, as it does in the more usual method of analysis by calendar years.

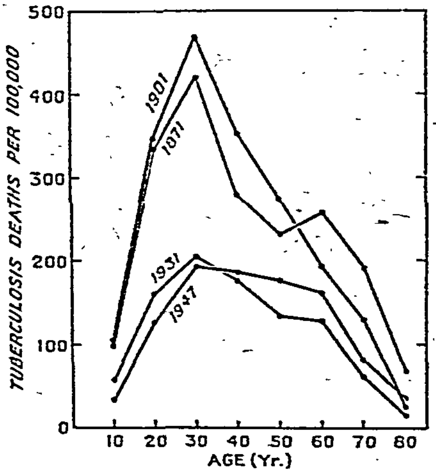

Fig. 8—Mortality from all forms of tuberculosis in Irish males.

There is little point in illustrating both methods of analysis for a large number of countries. It is sufficient to say that Frost's paper demonstrates a similar result for Massachusetts; Moine and Oudet (1947) have shown a similar consistency in the cohort distribution for Paris; Lancaster (1950) has shown the same effect with the rates for Australia; and Picken (1940) has published a similar analysis for the rates for England and Wales. In addition to citing some of these results, I have in an earlier paper (Springett 1950) analysed the rates for Scotland and the towns of Denmark, in which the shift of the peak occurs in males; and for Ireland, Norway, and Sweden, in which no shift occurs in either sex.

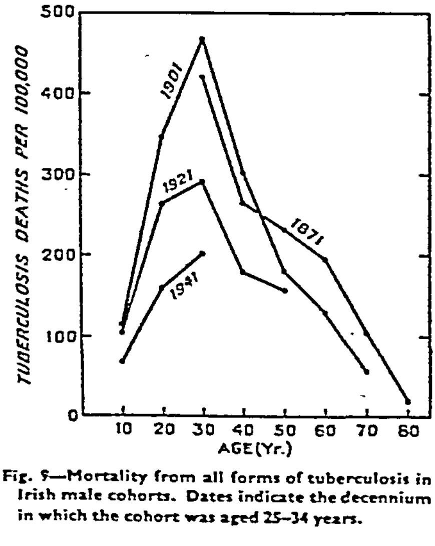

Fig. 9—Mortality from all forms of tuberculosis in Irish male cohorts. Dates indicate the decennium in which the cohort was aged 25–34 years.

Figs. 8 and 9 show the effect of applying this method of analysis to the rates of a country such as

Ireland, which, like Norway and Sweden, has shown no shift of the peak and only slight differences between the older age-groups of the two sexes. The rates have fallen greatly in Ireland during the period 1900–40. There is no shift of the peak, which is at 25–34 throughout, though the fall in rate with increase of age has become less rapid. If we study these rates for cohorts we find that the peak is again at the age of 25–34, and that the fall in the rate over that age is very steep indeed. Similarly, in Norway, the rates have fallen greatly, with no shift of the peak but with rather less difference between young adult and older ages. However, for cohorts, the difference between young adult and older ages is very great. The method does not, therefore, lead to an impossible or even an improbable result when applied to communities in which no shift of the peak has occurred.

So far, no more has been done than to demonstrate that a more constant age-distribution of mortality can be obtained by this method of analysis. It is necessary to assess the validity of the method and its clinical implications. So far as validity is concerned, it has been objected that study by cohorts is not justified, because improving conditions and treatment cause a cohort to experience increasingly favourable conditions as it becomes older, thus invalidating comparison. So far as chronic disease is concerned, does not this objection apply equally to the generally accepted method of analysis by calendar years? For the young in the year under consideration are experiencing better conditions than were experienced by the older persons with whom they are being compared.

One of the earliest papers on this method of analysis was by Derrick (1927); Greenwood (1927) was extremely critical of the method in the subsequent discussion, especially in so far as the method was to be used to forecast future rates. This criticism is, I think, fully justified. But when a retrospective analysis of rates already experienced is made, and a remarkable consistency is found by this method, I think it is justifiable to suppose that there may be some reason for the consistency and to try to seek it. Incidentally, it is interesting to forecast tuberculosis mortality-rates for older age-groups from the rates already experienced in younger age-groups, and not entirely discouraging. I do not, however, propose to pursue that line, because in the last few years new factors have come into operation, the long-term effects of which cannot be seen.

Daw (1950) has discussed the statistical aspects of this cohort method of analysis, the principle of which is to obtain a mathematical formula for the tuberculosis mortality of a group based on year of occurrence and year of birth. This is not the place to deal with that aspect, nor am I capable of doing so. The explanation of the more consistent distribution in cohorts is, I believe, medical rather than statistical, and I wish now to consider the medical implications of a more constant distribution in cohorts than in years.

For a disease that was always acute, leading to death or recovery in days, weeks, or at most a year, the cohort method of analysis could have little meaning. For an acute disease of this type the mortality-rate at any age must depend mainly on the attack-rate at that age in the same year. But for a disease, such as tuberculosis, which may cause death within a short interval of first infection or first illness, or only after a long illness with, perhaps, long periods of reasonably good health, the mortality-rate in later life could depend in part on the attack-rate experienced by the group when younger. It is conceivable that most cases of tuberculosis originate in early adult life. A proportion of those infected die while still young adults, but some survive to die after various intervals, which may be as long as 50 years. If tuberculosis does follow this course, it is reasonable for there to be a relation between tuberculosis mortality of older persons and that of the same group of persons when younger. For the young adult mortality is the " acu mortality, and conceivably a measure of the att rate; and it is this attack-rate that largely determine mortality of the group in older life.

The most likely alternative explanation for a l mortality-rate in older persons is a high attack-rat new disease at that age. In fact there is, or has b until quite recently, a tendency to assume that thi the only possible explanation—to take for granted t the high mortality-rate in older males is necessarily indication of a high attack-rate of new disease at this a

May I here make a non-medical parallel which m simplify the matter? If, for some obscure reason survey was made in which retired fellows of the Ro College of Physicians were asked " Have you ever dri through London in a horse-drawn cab?" I think likely that there would be a high percentage of posit answers. If, now, the same question were asked of rec licentiates of the college, I should expect a very l percentage of positive answers. Now a logical explar tion of this difference would be that driving throu London in a horse-drawn cab is a risk to which physici are exposed on their passage from qualification retirement; but it is far more probable that the differen is due to changes in methods of transport; and, indee this can be verified by revising our hypothetical surv question to "Have you, in the last year, driven through t streets of London in a horse-drawn cab?" when an equal low percentage would probably be obtained in each grou

The present high tuberculosis mortality in older mal is, I suggest, on a par with driving in a horse-drawn ca It is a relic of something this group of men experience as young adults. To establish the point for tuberculos it is necessary to obtain an answer to our second questic in the form " Have you developed pulmonary tuberculos in the past year?"—i.e., to obtain attack-rates of disease for various age-groups in recent years. This I attempted in a paper published a few months ago dealing with the results of repeated mass radiography of the same individuals (Springett 1951). Fig. 10 summarises the results obtained.

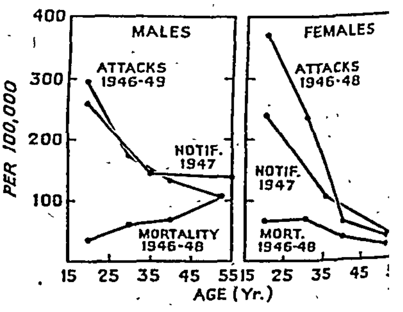

Fig. 10—Age and sex distribution of mortality rates, notification-rates, and attack-rates o pulmonary tuberculosis in England and Wale

The rates for women do not reveal any serious dis crepancies. Mortality-rates, attack-rates, and notifi cation-rates are all highest in early adult life, falling to lower levels in later life. The fall in the curve for mortality is less steep than for the other two curves, but all three rates follow the same general pattern.

For males the position is different. We have already seen that in recent years tuberculosis mortality of males has shown a peak late in life. The attack-rate—i.e., new cases developing in those previously normal—is very different, being highest in young adults and falling to fairly low levels in later life. The notification-rate follows a similar pattern to the attack-rate, being highest in young adults and falling, though less steeply than the attack-rate, to lower levels in later life. This discrepancy between attack-rates and notification-rates, on the one hand, and mortality-rates on the other, suggests that t present high mortality-rates in older males are no due to recently acquired disease; unless the new cas in older males are, on the whole, of a more serious typ with a higher proportion of acute fatalities than in th ounger age-groups. I have obtained some evidence on is point from the mass-radiography series, for the ew cases were divided into those that were stable r at least 6 months and those developing signs of ctivity within 6 months. Under the age of 35 the ctive cases outnumbered the stable (23 to 15); over he age of 35 the proportions were almost exactly reversed (4 active to 21 stable); that is to say, if there is any ifference between the age-groups in this respect, the endency is towards greater stability in the new cases eveloping in the older age-groups.

On the other hand, many mass-radiography surveys ave shown that there is a great reservoir of cases in lder males examined for the first time; in this ountry between 1% and 2% of those examined for the rst time in older age-groups show evidence of tuberculosis. In reviewing the cases for this mass-radiography tudy I was greatly impressed by cases recalled and ssessed inactive after a brief period of assessment at rst examination, who returned for a later examination vith obviously active disease, without receiving treatment or observation in the interval. Indeed, in the older males, active cases of this type were more numerous han "new" active cases, despite the very small number f "inactive" cases re-examined. This type of disease as been regarded as of little importance by some, but here is increasing recognition of the possibilities of breakdown in such cases.

There are, of course, cases in which tuberculosis is dequately arrested; but breakdown is possible, even robable, in a considerable proportion of long-standing ases in older males. When you add to these the "good hronics," of which every chest clinic can produce many xamples, there is no difficulty in appreciating that a rge part of the tuberculosis mortality in males in later fe is due to a final breakdown of disease originally equired many years earlier. This is not to say that resh disease never occurs in these older age-groups.

CONCLUSION

Despite the present form of the tuberculosis mortality urve, there has never yet been a group of men who xperienced a greater tuberculosis mortality at ages over 5 than they had experienced at young adult ages. The linical counterpart of this statement is that tuberculosis eaths in later life are usually, though not always, the esult of disease acquired many years earlier. They re comparatively seldom the result of recently acquired ases.

(To be concluded)

THE TREATMENT OF MATERNAL OBESITY

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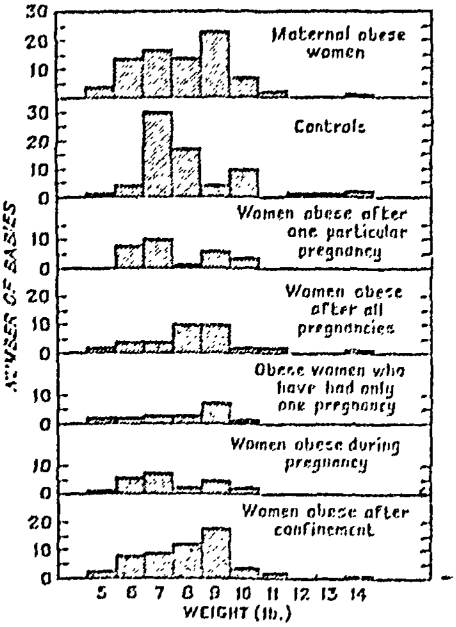
REMARKABLY little was written about maternal besity until Sheldon's paper appeared in 1949. Stimu- ted by that paper I have tried to collect information a similar way so that our results may be compared. his comparison is not altogether possible because eldon's was a planned experiment and my material s been drawn from a reference clinic designed for the eatment of unselected cases of obesity. I have, however, en able to look up the results of treatment in maternal esity, so as to compare them with the results obtained obese women who did not increase in weight with gnancy, and have looked for differences in the tion of the two groups to a standard method of tary restriction.

This report is concerned with 40 women who had eloped obesity during or immediately after preg- cy, and 30 obese women who had not done so. The smaller number of controls is due to the difficulty in finding examples in our records of women who did not get fat in relation to their pregnancies, and is, in a sense, evidence that maternal obesity is relatively common. Both groups are obese, but for simplicity I shall here refer to the maternal obesity cases as "obese" and the others as "controls."

TABLE I—INCIDENCE OF BIRTH WEIGHTS

	No. of women	Number of babies											Total no. of babies
		Birth weight (lb.)											
		4	5	6	7	8	9	10	11	12	13	14	
Maternal obesity ..	40	..	4	14	17	14	23	7	2	..	..	1	82
Controls	30	..	1	4	30	17	5	10	..	1	1	2	71
Type I:													
One particular pregnancy	9	..	..	8	10	1	6	4	..	..	..	..	29
Type II:													
All pregnancies ..	13	..	2	4	4	10	10	2	2	..	..	1	35
Type III:													
Only 1 pregnancy ..	18	..	2	2	3	3	7	1	..	..	..	..	18
During pregnancy ..	12	..	1	6	8	2	5	3	..	..	..	..	25
After pregnancy ..	28	..	3	8	9	12	18	4	2	..	..	1	57
Type I:													
During	4	..	..	5	6	..	2	2	..	..	..	..	15
After	5	..	..	3	4	1	4	2	..	..	..	..	14
Type II:													
During	2	..	..	..	1	2	1	..	..	..	..	..	4
After	11	..	2	4	3	8	9	2	2	..	..	1	31
Type III:													
During	6	..	1	1	1	..	2	1	..	..	..	..	6
After	12	..	1	1	2	3	5	..	..	..	..	..	12

After some thought it was decided to eliminate young uniparous women from the controls because there was no way of knowing whether they would subsequently develop maternal obesity. For this reason the control group is older. The average age of the obese was 33·9 years, and of the controls 45·1 years, when first seen in the clinic. For the same reason the average number of children born to the controls was rather higher than the number born to the obese. Most of the information collected is unaffected by this degree of selection; but, when treatment is discussed, this is not so; for, generally speaking, the older the patient the more difficult it is to reduce her weight.



Numbers of babies of different birth weights in different groups of obese women.

THE CHILDREN

The 40 women that developed obesity after one or more pregnancies bore 82 children, whereas the 30 controls bore 71. The average number of living children born to the obese was 2·05, whereas the average born to the controls was 2·37. The obese had 5 miscarriages (5·4%).

1 ectopic pregnancy (1·1%), and 5 stillbirths (5·4%) in 93 pregnancies. The controls had 7 miscarriages (8·9%) and 1 stillbirth (1·3%) in 79 pregnancies. The relatively high incidence of stillbirths in the obese compared with the controls agrees with Sheldon's (1949) findings.

Table I and the histogram show that, compared with the controls, the obese women bore more babies weighing over $8^{1}/_{2}$ lb. There were also more large babies born to mothers who became obese with each successive pregnancy than to those who became obese after one particular pregnancy, and these findings also resemble Sheldon's. In my series, however, fewer large babies were born to women who became obese during their pregnancy than to those who became obese after confinement; and in this it differs from his.

The four smallest babies born to the obese weighed $5-5^{1}/_{2}$ lb. Three of these were born to mothers who increased in weight after their delivery, and one to a mother who increased greatly during her pregnancy.

The sexes of the babies were equal in both the obese and the controls.

THE WOMEN

The women in both the maternal-obesity group and those getting obese later in life had the features of simple obesity in almost every instance. The increase in fat was generalised, with the greatest deposition in the places usual for women—i.e., over the breasts, the upper part of the buttocks and thighs, the back of the upper arms, and in a cape over the shoulders. In only 1 woman was the distribution characteristic of that found in Cushing's syndrome, and this was in a case of maternal obesity.

None of these women had glycosuria, and the sugar-tolerance curves obtained in a few of them were all normal. There was no difference in menstrual history, either before pregnancy or in the time of the return of menstruation after pregnancy, between the obese and the controls. There was no history of excessive lactation, but the two groups showed a striking difference in the numbers of children breast-fed. The 40 women who developed maternal obesity reared 82 children of whom 71 (86·6%) were breast-fed, whereas the 30 women whose obesity was unrelated to pregnancy reared 71 children of whom 39 (54·9%) were breast-fed.

The women with maternal obesity were heavier at the time of attending for treatment than the controls. Their average increase in weight above their calculated correct weight was 53·7%, whereas that of the controls was 42·5%. Their average weight before marriage was, however, less than that of the controls. 39 of the obese knew their pre-marriage weight: 30 (77%) were above their calculated correct weight, average 21·6 lb., and 9 below it, average 11 lb. 25 of the controls knew their pre-marriage weight: 19 (76%) were overweight, average 30·5 lb., and 6 underweight, average 15·8 lb. The percentage of women overweight was thus the same in the two groups, but the average increase before treatment was greater in the controls. These figures suggest that women who are overweight before marriage do not necessarily increase with their pregnancy; and, likewise, being underweight is no guarantee that maternal obesity will not develop. It is clear, nevertheless, that most women who become obese in relation to pregnancy are overweight before conception.

The gains in weight in my series were not so great as in Sheldon's. Three-quarters had gained between 20% and 60% over their pre-marriage weight (table II), whereas half of his had increased by 75%; but, as he points out, his was a sample referred to him in response to a special request to practitioners of the district for such cases. The greatest increase in my series was found in a case of maternal obesity. This woman had a pre-marriage weight of 7 st., which was 11 lb. under the calculated correct weight for her age and height. S had six children, the first five of whom weighed more th 9 lb., and the last 14 lb. She increased in weight af each pregnancy, and weighed 17 st. 7 lb. after the la an increase of 150%.

TABLE II—GAINS IN WEIGHT

Percentage gain (marriage weight = 100%)	10–20	21–30	31–40	41–50	51–60	61–70	71–80	81–90	91–100	101–110	Over 110
Maternal obesity ..	1	6	10	11	2	3	2	2	1	1	1
Controls	6	6	7	5	1	1	3	..	..	1	..

All the patients with maternal obesity had gain weight most rapidly at first, and half had reached a sta of equilibrium months or years before attending f treatment. The remaining half, after an initial rapid ri had continued to gain weight slowly but steadily. The was very little tendency to spontaneous reduction weight. The controls had, for the most part, gained weig steadily, with a more rapid rise shortly before comi for treatment. The onset of the rapid rise was oft related to an illness or an operation, a change of mode living, or some increase in nervous tension.

The onset of gain in weight in 28 (70%) of my seri was after confinement, and it was usually delayed f two or three months. The 12 (30%) women who began increase in weight during pregnancy did so in the fir half, between the third and fourth months. 30 wome breast-fed their children, and of these 19% develop their obesity during pregnancy and 81% after pre nancy, whereas, of those who did not breast-feed th children, 40% gained weight during pregnancy a 60% after it. The figures suggest that there may be mo trouble in establishing lactation in those who ga weight during their pregnancy than in those who ga after it. The onset of obesity in those who developed after delivery began with the onset of lactation in cases: on weaning the child in 1 case, and with t *return of menstruation in 2. As has already* been stat the majority did not begin to increase in weight for tv or three months.

Besides noting that maternal obesity may beg either during or soon after pregnancy, Sheldon observ that in some women obesity followed one specific pre nancy, whereas in others the weight went up with su cessive pregnancies. My findings support this vie After excluding the 18 women who had only one confin ment and thus could not be so divided, there were examples of those who gained weight with one particul pregnancy and 13 who gained with all pregnanci When a single pregnancy was followed by a gain in weig it was the first in 3 cases, the second in 2, the thi in 3, and the fifth in 1. The sexes of the children h no relation to the onset of obesity in this group, five bei girls and four boys, and in this my findings differ fro Sheldon's. When obesity followed successive pregnanc it developed after the first and each succeeding one every instance, and again the sexes of the children we equally divided.

20 women with maternal obesity know their own birt weights, and of these 5 were 10 lb. or over. Unfor-tunately only 9 of the controls knew their birth weight and of these 2 were 10 lb. or over.

FAMILY HISTORY

36 patients with maternal obesity and 17 control knew whether their mothers had become obese in relati to childbearing. 17 of the mothers of the obese had gained (47·2%), a figure that contrasts sharply with t of 5·9% for the mothers of the controls.

The sisters of 12 of the 37 obese women who k about them had developed maternal obesity.

oman had five sisters all of whom reacted in this way. Their mother, who was initially slim, reached 20 st. at the age of 35 as a result of maternal obesity that increased with each pregnancy.

Unfortunately the histories of the controls are inadequate, and the percentage of their sisters who became it as a result of pregnancy is unknown.

DIETARY HISTORY

Dietetic histories were taken from all the obese women by a dietitian, but their accuracy is doubtful and definite conclusions cannot be drawn. It seems clear that there was no demonstrable difference between the total calorie intake in the two groups during pregnancy, because the ange of calorie intake for the maternal obese cases was 1450–3400, with most cases lying between 1600 and 2300 calories, while the controls had a range of 1354–3880 calories, with, again, most cases taking between 1600 and 2300 calories daily. There was, however, a difference in the ratio of intake of carbohydrates to protein and fat in the two groups. The women with maternal obesity had an average carbohydrate/protein/fat ratio of 4·1/1/0·9, whereas the corresponding ratio in the controls was 4·2/1/1. There was thus a relatively higher intake of fat and protein in the maternal obese women.

In their eating habits these women fell into two groups: some distributed their calorie intake throughout four meals in the day, and others took very little apart from one really large meal. Whereas 70% of the women with maternal obesity ate normal meals at the usual times, 73% of the controls had a single large meal and very little else.

DISCUSSION

No attempt will be made to discuss the production of maternal obesity or its relation to the "large baby diabetic syndrome"; for this has been done recently by Sheldon (1949). The present findings, however, tend to confirm his suggestion that there are differences between women who get fat in relation to pregnancy and those who do not.

Obesity may first appear during pregnancy at about the third or fourth month, or after delivery, usually about two or three months later, and it may increase with each uccessive pregnancy or follow only one. In my series the women who became obese with each pregnancy had the largest babies, and it will be of interest to know whether they develop diabetes mellitus in later life. There are, however, examples of small babies being born to mothers who got very heavy indeed with their pregnancy.

The establishment or ending of lactation seems to have no bearing on the onset of obesity, but lactation itself does. Compared with the controls, more women with maternal obesity fed their babies. Among the maternal obesity cases the majority increased in weight after delivery, and compared with the remainder who gained weight during pregnancy, these more often breast-fed their children. This relationship of breast-feeding is far from invariable, because 25% of our women with maternal obesity did not feed their children, and 19% of those who did so became fat during pregnancy—i.e., before the onset of lactation.

When an attempt is made to determine which pregnant women are most likely to get fat, a history of maternal obesity in their mothers, a tendency to be overweight before marriage (77% of cases), and a high birth weight are of some significance. When a woman has reached elivery without becoming obese, the presence of any f the above factors, coupled with the satisfactory establishment of breast-feeding, should lead to advice about her calorie intake, especially as the second month is approaching.

TREATMENT

Both groups were, of course, treated in the same way. They were given a standard 1200-calorie reducing diet, with amphetamine ('Benzedrine' or 'Dexedrine') in 5 mg. doses an hour before breakfast and their midday meal. They attended for regular weighing and discussions with a dietitian, usually once a week but in some cases once a fortnight. They were all seen and medically examined at regular six-week intervals. Thyroid and diuretics were never used.

TABLE III—RESULTS OF DIETETIC TREATMENT OF OBESITY

Weight class	Over-weight (%)	Age (yr.)		No. of women	Diet + benzedrine or dexedrine		
		Range	Average		Av. duration of treatment (mos.)	Av. total loss of weight (lb.)	Av. loss of weight per month (lb.)
Maternal obesity:							
I	1–20	..	..	Nil	..	..	..
II	21–40	22–54	34	8	6·7	13·2	1·9
III	41–60	22–54	34	18	8·8	25·8	2·9
IV	61–80	22–43	33	12	6·2	30·9	4·9
V	Over 80	42–54	48	2	3·0	38·5	12·8
Controls:							
I	1–20	35–73	51	7	5·7	11·0	1·9
II	21–40	26–56	42	7	4·5	23·4	5·2
III	41–60	30–54	41	10	5·9	21·7	3·7
IV	61–80	38–51	44	3	3·0	13·3	4·4
V	Over 80	37–55	47	3	2·6	25·6	9·8

It will have been seen that the average age of the controls was greater than that of the maternal obese, a factor that weighs against the success of the treatment of the controls. The average length of treatment for the obese women was 7·4 months, and of the controls 5·2 months. In spite of this (see table III) the controls reduced their weight rather better than those of the maternal obese whose overweight was less than 60% at the beginning of treatment; but where the overweight was 61–80% the maternal obese reduced better. The average rate of reduction per month was more rapid in the controls when the overweight was less than 60%, but above this level the rate of loss was about the same in both groups. It therefore seems that, when the women were very grossly overweight, there was no difference between the two groups in the rate or in the amount of reduction; but where this increase was moderate (60% or less) the controls lost rather more weight more quickly.

An additional difficulty in reducing the maternal obese compared with the controls was that they were already taking proportionately less carbohydrate, and thus the simple instruction to reduce their intake of potatoes, bread, and sugar did not suffice in the same way as it sometimes does in other cases. Again, a useful result was sometimes achieved by redistributing the calorie intake throughout the day in those who took one large meal, and this could only be done in few cases of maternal obesity, because their eating habits were, for the most part, regular.

There were three main ways in which the patients responded to dietetic treatment. Some showed an initial loss that was rapid for the first few weeks and then slowed to a loss of a few ounces a month. Others had a rapid initial loss followed by a small gain and then a slow loss. Others again had a steady fall all the time. And in a few there was no appreciable loss at any time. The rapid initial loss occurred in four-fifths (82%) of the women with maternal obesity, and in half (47%) of the controls. A tenth (11%) of the obese reduced slowly all the time, compared with half (47%) of the controls, and a few in each group did not lose weight at all (see table IV).

The rapid initial loss in the maternal obese may be explained in more than one way.

It may be that here the age of the women makes a difference, the younger ones being more anxious to lose weight, initially more enthusiastic, and thus strictly

TABLE IV—RESULTS OF DIETING

Group	With rapid initial loss (%)	With slow steady loss (%)	With no loss (%)
Maternal obese (40)..	82	11	6
Controls (30) ..	47	47	5

keeping to their diet. This may not be the whole answer, because the diet, at 1200 calories, is a generous one for a reducing diet, and rapid losses are thus not to be expected with it; likewise, steady reduction is improbable unless the instructions are closely followed. It is suggested rather that fluid retention may play a larger part in maternal obesity than in the controls because, although no attempt was made to restrict fluid as such, some restriction usually takes place: less tea is drunk while on the diet and all sweetened or alcoholic drinks are barred. The small rise that sometimes follows the initial fall may be due to rehydration through acquiring the habit of drinking plain water, and the downward trend could perhaps be restarted more quickly by the use of diuretics. If this is the true explanation, it supports Sheldon's suggestion that these women have some disturbance of the hypothalamus. It is well known that obesity has followed experimental damage to the hypothalamus in animals, and that the hypothalamus is concerned in maintaining the fluid balance of the body.

Whatever the explanation, this rapid initial loss is followed by a slowing that makes the average total time for satisfactory reduction longer than in women who do not become obese with their pregnancy, and discouragement—the greatest enemy of reduction—can easily develop.

The dietitian and the doctor must therefore be prepared to expend even more energy in exhortation and moral support when the onset of the obesity is related to pregnancy than when it is not.

SUMMARY OF CHARACTERISTICS OF MOTHERS WITH MATERNAL OBESITY AND THEIR CHILDREN

The babies of women with maternal obesity were larger than those of the controls, but the sexes were equal in both groups.

The number of stillbirths was higher from the women with maternal obesity: obese, 5 stillbirths (5·4%); controls, 1 stillbirth (1·3%).

77% of women with maternal obesity were overweight before marriage, and 76% of obese controls. The average amount of overweight was higher in the controls.

The women with maternal obesity developed a greater degree of obesity than did the controls (53·7% compared with 42·5% of their calculated correct weight).

Compared with the mothers of the controls the mothers of the maternal obese had more often suffered from maternal obesity.

The maternal obese put on weight either during or after pregnancy. The babies born to those who became fat during their pregnancy were no larger than the babies born to those who became fat after their pregnancy. Breast-feeding was less among mothers who became fat during pregnancy than among those who became fat after pregnancy (19% during and 81% after).

Of the 40 women with maternal obesity 13 (32·5%) became fat with the birth of each child, and 9 (22·5%) after one specific pregnancy. The other 18 (45%) had only one pregnancy.

The association with breast-feeding appears significant: 86·6% of the babies of the maternal obese were breast-fed, compared with 54·9% of the babies of the controls.

There were no great differences between the two groups in their response to treatment, but the controls reduced weight rather better and quicker when gauged in monthly periods than did the maternal obese. The latter, howeve lost weight more rapidly at first—perhaps through l of fluid.

To achieve a satisfactory reduction of weight in a ca of maternal obesity, much encouragement is requir from the dietitian and the doctor.

CONCLUSION

It is suggested that where there is a history of matern obesity in the patient's mother, or the patient had a lar birth weight or was overweight at the time of marriag maternal obesity should be expected and guard against by controlling the diet in the early months pregnancy.

Where any of the above factors, more particular combinations of them, are present, and obesity has n developed by the time of delivery, care should be tak to avoid excessive caloric intake during the first f months after it. This is especially important if th mother is breast-feeding the infant, because she is ofte induced, only too easily, to eat too much "for the sa of the child."

When maternal obesity is established, its treatmen with diet may be more difficult than the treatment o other forms of obesity. An initial rapid fall, possibly du to fluid loss, is followed by a difficult period during whic loss is very slow or in which weight may be gained, an discouragement can easily ensue.

My thanks are due to Mrs. M. Walwyn-Jones for her he and coöperation, especially for taking the dietary histories.

REFERENCE

Sheldon, J. H. (1949) *Lancet*, ii, 860.

EYE CHANGES FOLLOWING EXPOSURE T METALLIC MERCURY*

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With illustrations on coloured plate

DURING an investigation into the incidence of metalli mercury poisoning among repairers of direct-curre electric motors in the London area (Bidstrup, Bonnel Harvey, and Locket 1951) the eyes of an unselecte group were examined. This was done in order to fin out if there were any eye changes and, also, whethe the appearance of the lens resembled that described b Atkinson (1943) and Atkinson and von Sallmann (1946

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* Based on work carried out in a survey by the Department Research in Industrial Medicine of the Medical Resear Council; for a full report on the remainder of this work Bidstrup et al. (1951).

LEGENDS TO ILLUSTRATIONS ON PLATE

DR. LOCKET, MR. NAZROO

Appearance of anterior surface of lens after long exposure metallic mercury

A is a normal eye; the white narrow zone is the normal appearance of anterior surface of the lens as seen in the slit-lamp beam. B and D s moderate pigmentation of this zone, and C shows marked pigmentation.

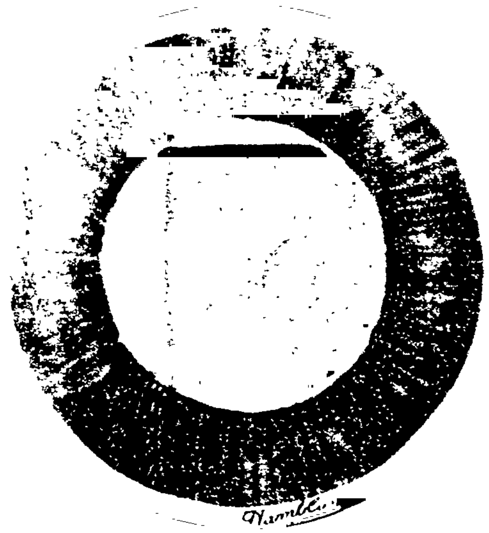
DR. DREYER, DR. BUDTZ-OLSEN

Fig. 1—Splenic venogram showing diodone in splenic vein and p vein in a case in which the portal circulation was normal. N filling defect at junction of splenic vein with superior mesent vein.

Fig. 2—Splenic venogram in a case of thrombosis of splenic vein, sho complete absence of radio-opaque material from splenic vein, diodone passing through anastomosing left gastric and short g veins to portal vein.

DR. LOCKET AND MR. NAZROO: MERCURY AND THE EYE

A



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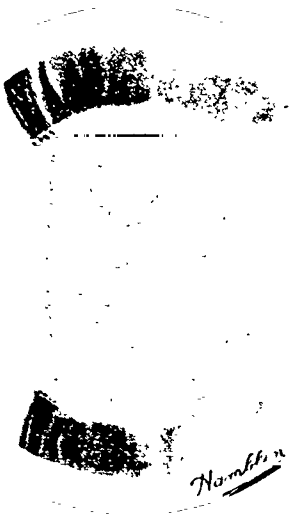

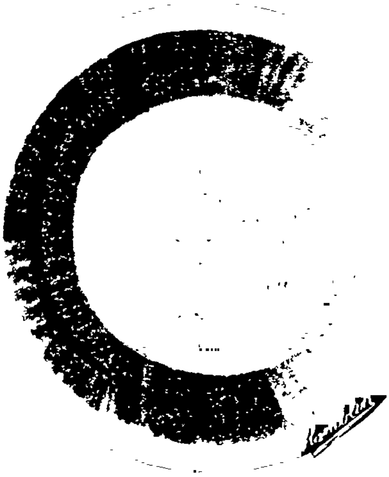

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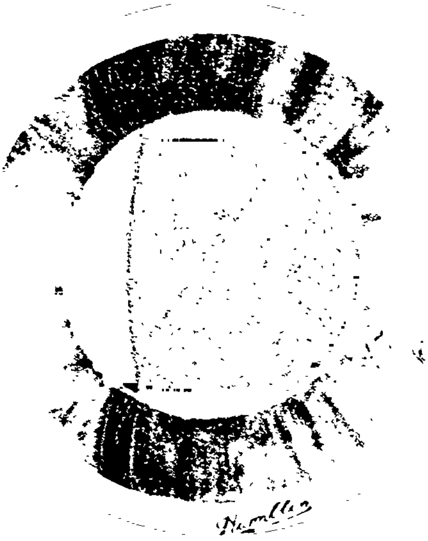

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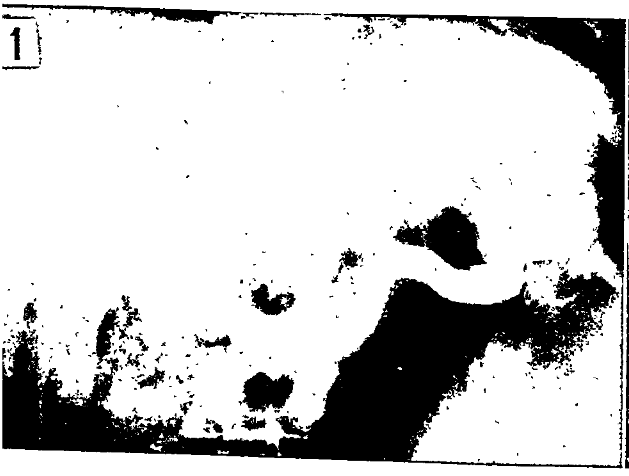
DR. DREYER AND DR. BUDTZ-OLSEN: SPLENIC VENOGRAPHY



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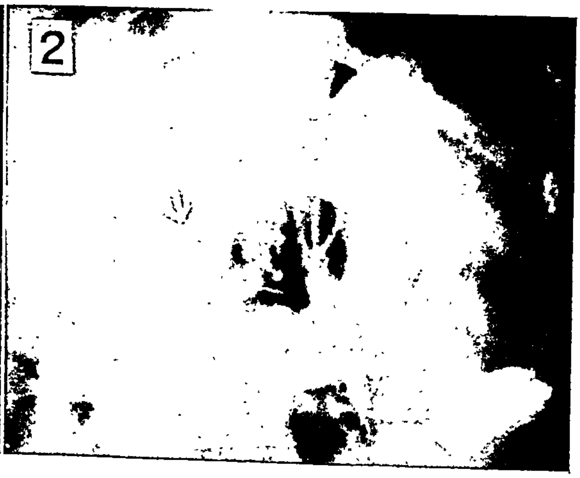

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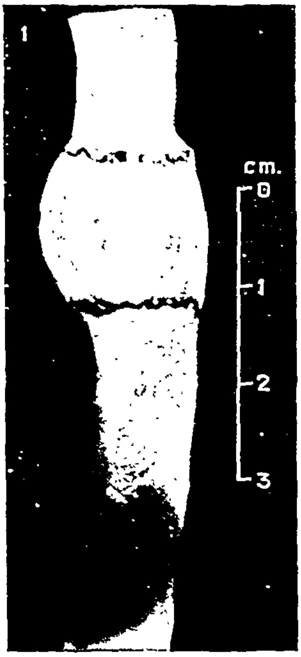
PROF. HUFNAGEL, MR. EASTCOTT: PRESERVATION OF ARTERIAL GRAFTS BY FREEZING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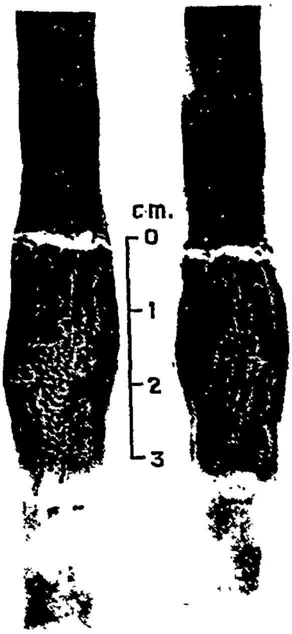
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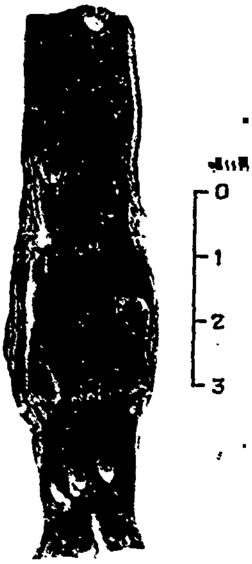
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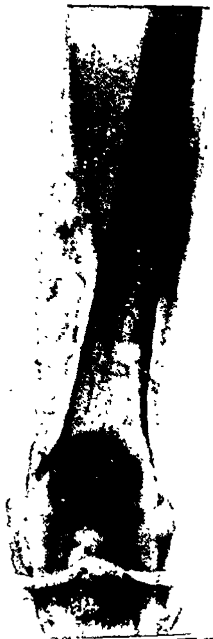
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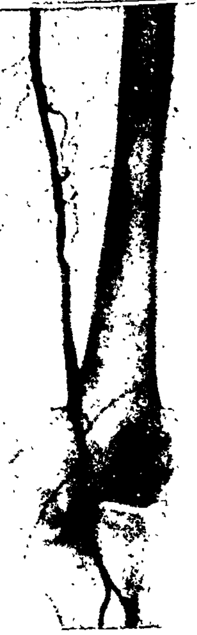
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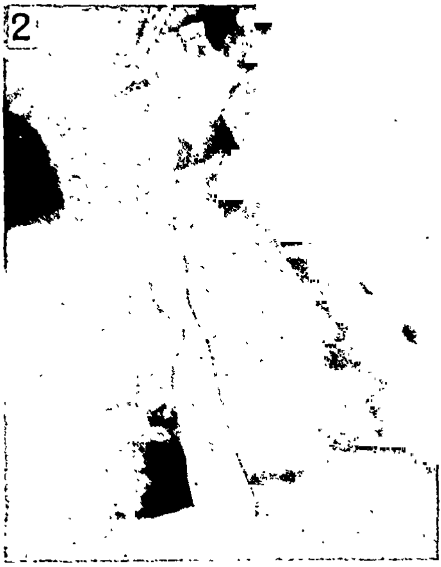
MR. DOLTON, DR. EVERLEY JONES: ANOMALIES OF AORTIC ARCH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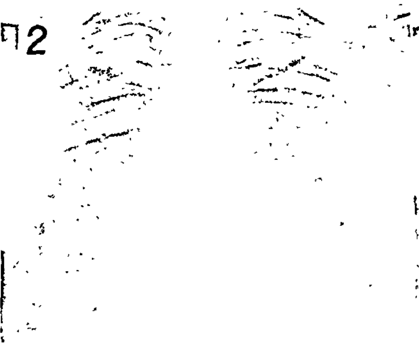
3

DR. FISHER, DR. MAKIN: PULMONARY HÆMOSIDEROSIS

1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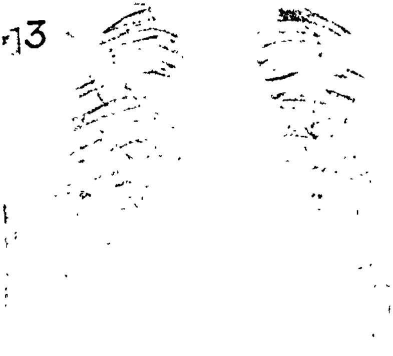
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METHOD

f the 161 meter repairers who attended at the London pital for full clinical and laboratory examination, selected at random were examined at Oldchurch pital, Romford. The eyes were examined for n and muscle balance, and focal examinations by e and slit lamp were made. Visual fields were care- y plotted by perimetry, and the retinæ examined ı the ophthalmoscope.

f the 51 meter repairers so examined, 2 whose ages e not ascertained have been omitted from the group se results are analysed here. The remainder were d 20-60 years, and all were males.

RESULTS

n no case was there any evidence of retrobulbar ritis, and visual fields were in all cases within normal its. Fundal changes were minimal, and these were eriosclerotic when present, and only occurred in those d 40-60, being no more frequent than in any comable group of adults of this age. One man had t-traumatic phthisis bulbi of one eye.

iplopia was not complained of, and in no case did we l nystagmus or evidence of muscle imbalance.

n 29 cases obvious changes were seen in the lens, nea, and limbus. It was possible to divide these nges into three main categories:

1) Brown reflex from anterior lens capsule. This reflex s bilateral and symmetrical in all cases and varied in ensity from light brown to coffee brown (see illustrations).

2) Fine punctate opacities in the lens. These occurred all depths, but usually were most evident in the anterior tex of the lens. They were always bilateral.

3) Well-marked vascularity at corneoscleral junction, with en the appearance of empty vessels, the effect being on the ole that the aqueous veins were brought into prominence, well as the fine vascular loops seen in this region normally.

ge (yr.)	No. of persons	Brown lens reflex	Lens opacities	Vessels at limbus
20-30	17	1	5	8
30-40	12	3	—	6
40-50	9	2	2	4
50-60	11	6	3	5
otal ..	49	12	10	23

Each of these three types occurred either alone or association with one or both the other changes described d were always bilateral, even in the man with post-aumatic phthisis bulbi of the left eye.

The 49 workers were divided into four age-groups, and the incidence of the changes in each of these groups is shown in the accompanying table. It will be seen that the brown reflex from the anterior lens capsule occurred most frequently in the oldest age-group.

DISCUSSION

In this group of 49 meter repairers handling mercury, exposure to metallic mercury ranged from thirty-nine years to less than a year. Of the 12 men with a brown reflex from the anterior lens capsule none had been exposed to mercury for less than five years, and 9 of these had been exposed for more than fifteen years. Atkinson (1943) reports 1 case only with exposure of less than five years. In the age-group 50-60, 7 out of 11 had been exposed to mercury for more than fifteen years, and 6 of these 7 showed this brown coloration, whereas of the remaining 4 in this age-group (3 with exposures ranging from nine months to three years) none showed this change. It thus seems that the brown reflex of the anterior lens capsule does not depend on duration of exposure alone, since many men who had long been exposed to mercury did not show it; though it is closely related to this duration since it was found at all ages, but no case occurred after an exposure of less than five years. These findings suggest that a definite minimal atmospheric concentration of metallic mercury, as well as a minimal duration of effective exposure, is necessary to produce the brown reflex.

The brown reflex of the anterior lens capsule is not related to age alone, since in the oldest group it only occurred in those with exposures of fifteen years or more.

These conclusions can only be considered as suggestive, since the groups are not big enough for detailed statistical analysis.

Neither lens-opacities nor limbal vessels showed any relation to duration of exposure, since they were evenly distributed in the group from seven months' exposure to thirty-nine years.

Of the 15 men in this eye group who showed clinical evidence of mercury poisoning at the time of examination, 4 showed the brown reflex of the anterior lens capsule, 3 showed lens opacities, and 3 the limbal vessels. There is therefore no relation between clinical evidence of mercury intoxication at the time of examination and any of these eye changes.

It thus seems that the brown reflex from the anterior lens capsule is related to length of time the worker has been exposed to mercury in any concentration, probably above a certain, though unascertainable, minimum. It is not necessarily due to exposure to high levels for a short time, for were this true we would have expected a higher incidence of this lens change in patients with evidence of mercury poisoning at the time of examination.

One of the men after fifteen years' exposure had not been in contact with metallic mercury for about four years, yet his anterior lens capsule still showed this brown reflex.

We could detect no evidence at all in any case to suggest that this brown reflex of the anterior lens capsule was the cause of any visual symptoms or might lead to more serious ocular disturbance.

One patient had phthisis bulbi of his left eye, which was probably post-traumatic. Nevertheless his anterior lens capsule showed this brown reflex, which was identical in intensity with the brown reflex in his good eye.

We also found eye changes of a different kind in some cases of metallic mercury poisoning seen before the present investigation and not included in this series. Clinical and biochemical details of these cases are cited fully in the report by Bidstrup et al. (1951).

A patient with severe mercury poisoning, possibly mainly due to accidental ingestion of metallic mercury,

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LEGENDS TO ILLUSTRATIONS ON PLATE

PROF. HUFNAGEL, MR. EASTCOTT

g. 1—112-day frozen carotid homograft immediately after removal, showing passive condition of graft and compaction of host segments.

g. 2—Frozen carotid homografts taken from the same animal at the 111th postoperative day.

g. 8—Quick-frozen aortic homograft exposed *on the 67th day.*

g. 9—Left femoral arteriogram showing occlusion of popliteal artery.

g. 10—Left femoral arteriogram 14 days after insertion of frozen arterial homograft.

MR. DOLTON, DR. EVERLEY JONES

g. 2—Radiograph after barium swallow, showing anterior and posterior constriction of œsophagus at level of fourth thoracic vertebra.

g. 3—Angiocardiogram of double aortic arch.

DR. FISHER, DR. MAKIN

g. 1—Bilateral middle zone opacities of pulmonary œdema, March, 1949.

g. 2—Diffuse mottling and left pleural effusion, November, 1949.

g. 3—Established hæmosiderosis and right pleural effusion, March, 1951.

was admitted to Oldchurch Hospital under the care of one of us (S. L.). In this case we found doubtful nystagmus, retinal œdema, diplopia, and gross muscle imbalance, but no brown reflex of the anterior lens capsule. In yet another of the patients with mercury poisoning, seen at Oldchurch Hospital (S. L.), inability to accommodate, and blurred vision on awakening in the morning, disappearing by midday were the presenting symptoms.

The symptoms and eye changes in both these patients disappeared some weeks after clinical evidence of mercury poisoning had ceased. This response was quite unlike that of the brown reflex, which is, in our opinion, evidence of protracted exposure only, and persists unchanged for years after removal from mercury exposure.

It would be interesting to speculate on the cause of these eye changes. Atkinson and von Sallmann (1946) believe there is an actual deposit of mercury on the lens and have apparently proved this in one case at necropsy. How the mercury is absorbed so that it can be deposited in this fashion is very difficult to imagine, in view of its absence after mercury absorption and intoxication in other groups of cases. Direct absorption via the eyes seems to be the only possible explanation of the coloured reflex in these chronically exposed subjects. Other ocular changes in intoxications, as described above, are, however, almost certainly due to the action of mercury or some organic compound of mercury on the ganglion cells of the central nervous system and possibly on more peripheral ganglia. In some respects the tremor and emotional charges in mercury poisoning resemble those of parkinsonism, but when gross may easily be mistaken for disseminated sclerosis.

We suggest that this lens change could be used as a screening process to eliminate the possibility of long-continued exposure to low levels of atmospheric metallic mercury, just as clinical evidence of intoxication would suggest higher atmospheric levels or a more severe breakdown in precautionary measures. Routine annual inspection of the lens would give the necessary warning and might call for full air-level studies.

Although this lens appearance is not apparently associated with any permanent ocular damage, we nevertheless feel that these changes are abnormal and undesirable and that everything should be done to prevent them.

SUMMARY

Among 51 repairers of direct-current electric meters who handled metallic mercury and were examined for eye changes, 12 showed a matt-brown reflex from the anterior lens capsule.

This change seems to depend mainly on length of exposure to metallic mercury, and is not related to symptoms of mercury intoxication at the time of examination.

In all cases this brown reflex was bilateral and apparently had no effect on visual acuity.

No evidence of retrobulbar neuritis was found in any of the 51 workers examined.

It is suggested that this coloured reflex from the lens could be used as a screening device for atmospheric mercury levels.

We wish to thank Dr. Donald Hunter for his help and the facilities offered by his department; Dr. P. Lesley Bidstrup and Dr. J. A. Bonnell, of the department of research in industrial medicine at the London Hospital, for their coöperation in this investigation; Dr. H. Wyers and Dr. J. Graham, S.A.M.O., of the N.E. Metropolitan Regional Hospital Board, for their help and guidance at the commencement of this work; and Mr. A. A. Hilfer, of Theodore Hamblin Ltd., for his coloured drawings of the eyes.

REFERENCES

Atkinson, W. S. (1943) *Amer. J. Ophthal.* 26, 685.
— von Sallmann, L. (1946) *Trans. Amer. ophthal. Soc.* 44, 65.
Bidstrup, P. L., Bonnell, J. A., Harvey, D. G., Locket S. (1951) *Lancet*, ii, 856.

SPLENIC VENOGRAPHY

DEMONSTRATION OF THE PORTAL CIRCULATION WITH DIODONE

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With illustrations on plate

THE anastomoses now used for the relief of portal hypertension depend for their success on exact localisation of the obstruction.

Several indirect methods of estimating the pressure in the portal system have been suggested—e.g., the rate of absorption of acetylene (Henning et al. 1950) or dyes (Souidan 1950) from the intestinal tract—but only after opening the abdomen has the surgeon been able to look for the obstruction, either by multiple venous-pressure readings (Blakemore and Lord 1945, Blalock 1947) or by the injection of diodone into the splenic vein or its tributaries (Whipple 1945). These manipulations prolong the operation undesirably and demand considerable team organisation.

We describe here a method by which the splenic vein and part of the portal circulation can be examined before operation, and the site of obstruction demonstrated in cases of portal hypertension.

METHOD

The patient is fasted and given a mild hypnotic to allay apprehension. He is placed supine on an X-ray table. The skin over the splenic area is cleaned, and the tissues in the 9th intercostal space are infiltrated with a local anæsthetic. A small lumbar-puncture needle is attached to a syringe containing 20 ml. of 70% diodone heated to body-temperature. The patient is told to hold his breath; the needle is pushed medially, and slightly posteriorly, through the 9th intercostal space into the spleen, the engagement of the organ being usually distinctly felt; and the dye is rapidly injected. The X-ray exposure is made towards the end, but before the completion, of the injection.

RESULTS AND APPLICATIONS

This procedure has now been applied in eleven cases without untoward incident. The spleen was palpable in all of them. Two of them subsequently came to operation, and no tear or other gross lesion of the spleen was found. On one occasion the patient could not hold his breath, but no harm resulted. The intraperitoneal injection of diodone produces no reaction in animals and is apparently also harmless in man.

A radiogram from a case with normal portal circulation is shown in fig. 1. The "filling defect" or dilution of the dye at the junction of the splenic and superior mesenteric veins is clearly seen.

Some interesting features of the physiology of the spleen have emerged during the development of this method:

(1) The great rapidity with which the diodone leaves the spleen (2 seconds or less) supports the conception of an "open" splenic circulation (MacKenzie et al. 1941) and opposes the "closed" circulation hypothesis of Knisely (1936).

(2) The diodone does not diffuse throughout the splenic pulp. The spleen seems to work in distinct compartments draining into the splenic vein near the hilus (Douglass et al. 1950).

(3) Fig. 1 and similar radiograms taken during the preliminary experimental work on dogs throw doubt on the idea of "stream-lining" in the portal blood-flow; the radio-opaque material fills the whole liver and can certainly be seen

n the right lobe in fig. 1. This confirms the findings of Daniel ınd Prichard (1951), who showed that 'Thorotrast' injected nto a branch of the superior mesenteric vein in different aboratory animals perfused the whole liver.

Several clinical applications of this simple method suggest themselves. The demonstration of the intrahepatic circulation may be of diagnostic significance in obscure hepatomegaly. The patency of a portocaval anastomosis may be demonstrated. (This has been done experimentally in dogs, but no opportunity has yet arisen in man.) The main value, however, will be in portal hypertension, in which the splenic venogram differentiates between intrahepatic and extrahepatic obstructions and may thus be the deciding factor in the treatment to be adopted, as in the following illustrative case.

CASE-RECORD

A Nyasaland Bantu male, aged 29, presented with a history of two attacks of malaria, the first 15 and the second 5 years previously. Three months before admission he had two small hæmatemeses a week apart, but at the time no lesion in his stomach or his duodenum was detected by radiography. Two more hæmatemeses occurred, the last 10 days before admission.

On examination he was pale (hæmatocrit 15%) and his enlarged smooth firm non-tender spleen was felt 3 in. below the costal margin.

Radiography now revealed a normal œsophagus, but there was considerable hypertrophy of the mucosa at the cardiac end of the stomach.

Splenic venography (fig. 2) showed complete obstruction of the splenic vein, with the radio-opaque material reaching the portal vein via anastomosing short gastric and left gastric veins.

Liver-function tests gave slightly abnormal values.

Operation was therefore at first deferred, but a month after admission profuse hæmatemesis recurred and an emergency splenectomy was carried out. At operation the thrombosis of the splenic vein and the gross dilatation of the gastric veins were confirmed.

Biopsy.—The histological appearance of the spleen was that of portal hypertension, and a specimen of the liver showed degeneration of liver cells, atrophy of cells with pigmentation, pigment within Kupffer cells, hyperplasia of cells, minimal fibrosis, and bile-duct proliferation. From the specimen neither postnecrotic fibrosis nor cirrhosis of the liver could be diagnosed.

Postoperative recovery was uneventful, and there has been no further hæmatemesis; but three months after the splenectomy the liver-function tests still gave abnormal results; so the ultimate prognosis must remain in doubt.

In this case the splenic venogram indicated clearly what the surgeon could expect to find at operation: obstruction of the splenic vein and dilatation of the gastric veins, including the submucosal veins (the "hypertrophied mucosa" of the radiologist), but no œsophageal varices, because the gastric veins drained back into the portal circulation. These predictions were confirmed.

SUMMARY

A method is described for the visual demonstration of the splenic and part of the portal circulation by the injection of radio-opaque material into the spleen without laparotomy.

Several uses of the method are indicated, and its value is shown in a case of thrombosis of the splenic vein.

Our thanks are due to Dr. L. Mirvish and Mr. G. Sacks for permission to publish this case.

REFERENCES

Blakemore, A. H., Lord, J. W. jun. (1945) *Ann. Surg.* 122, 476.
Blalock, A. (1947) *Ibid.* 125, 129.
Daniel, P. M., Prichard, M. M. L. (1951) *J. Physiol.* 114, 521.
Douglass, B. E., Baggenstoss, A. H., Hollinshead, W. H. (1950) *Surg. Gynec. Obstet.* 91, 562.
Henning, N., Demling, L., Kinzlmeier, H. (1950) *Dtsch. Arch. klin. Med.* 197, 288.
Knisely, M. H. (1936) *Anat. Rec.* 65, 23, 131.
MacKenzie, D. W. jun., Whipple, A. O., Wintersteiner, M. P. (1941) *Amer. J. Anat.* 68, 397.
ouldan, M. Z. A. (1950) *J. R. Egypt. med. Ass.* 33, 527.
Whipple, A. O. (1945) *Ann. Surg.* 122, 449.

THE PRESERVATION OF ARTERIAL GRAFTS BY FREEZING

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With illustrations on plate

In classical experiments Carrel (1908, 1910, 1912) and Guthrie (1912) proved that homologous vascular grafts can be used to restore arterial defects. Renewed interest in tissue transplantation, and developments in cardiovascular and cancer surgery, have led to further examination of the processes of arterial homografting.

The methods now in use for storing segments of blood-vessels depend on refrigeration at temperatures above freezing-point (Gross et al. 1949). At this temperature, however, death and chemical denaturation are usual after 3 or 4 weeks. We therefore considered the possible advantages of frozen arterial grafts (Hufnagel 1947; 1948).

The concept that frozen tissues might be kept for long periods in a condition suitable for surgical use has been the subject of several investigations.

Keith (1934) found that some bone cells survived freezing in a brass cylinder placed in liquid air. He observed new bone formation in the site of the transplants.

Mider and Morton (1939) froze normal rat skin at the temperature of solid carbon dioxide methyl-cellosolve mixture and found proliferation within the transplanted grafts at the 10th day.

Weiss and Taylor (1943) successfully used nerves frozen in liquid nitrogen, and then dehydrated, to bridge defects in rats, cats, and monkeys.

Webster (1944), employing a freeze-drying technique at −72°C for the preparation of split skin grafts, obtained 80% of takes in a patient receiving his own skin. Strumia and Hodge (1945) reached a similar result using skin which had been quite slowly frozen at −20° to −25°C.

Katzin (1947), in a review of corneal preservation, says that while quick-frozen transplants healed well, clouding invariably occurred at some stage of the freezing or soon after the operation. His article refers to earlier Russian work on cell survival in such grafts by tissue culture.

Garber and Bush (1950) describe their work on the use of frozen homologous bone which they banked and used routinely in suitable patients.

The principle was applied to vascular repair by Blakemore and Lord (1945) who employed homologous and heterologous vein segments which had been frozen and stored in sealed glass tubes. Several arterial defects were successfully bridged in this way. Hufnagel (1947) reported satisfactory results in a series of experimental frozen abdominal aortic homografts, using helium-filled tubes at −70°C. He again (1948) reported no failures in a series of twenty frozen thoracic aortic homografts using a temporary intubation method. Gross et al. (1949), in repeating these experiments on the abdominal aorta, found that the grafts were difficult to handle and that their use was attended by a high failure-rate due to a breakdown or thrombosis. Deterling et al. (1951) used a similar technique with satisfactory functional results though none of the grafts survived the freezing process.

TABLE I—AORTIC HOMOGRAFTS

Method of Freezing	Duration and temp. of storage	Period of observation (days)	Result
RAPID FREEZING			
Sucrose 18 hr. Liq. N₂ 74 min.	4 days −70°C	165	Patent
Liq. N₂ 5 min.	5 ,, ,,	159	,,
,, ,, 10 sec.	3 ,, ,,	60	,,
,, ,, 10 ,,	41 ,, ,,	127	,,
,, ,, 5 min.	63 ,, ,,	100	,,*
,, ,, 5 ,,	65 ,, ,,	10	Hæmorrhage†
,, ,, 10 sec.	14 ,, ,,	115	Patent
,, ,, 15 ,,	30 ,, ,,	103	,,
,, ,, 10 ,,	40 ,, ,,	90	,,
,, ,, 15 ,,	60 ,, ,,	51	,,
,, ,, 15 ,,	51 ,, ,,	87	,,
,, ,, 15 ,,	70 ,, ,,	67	,,
,, ,, 15 ,,	10 ,, ,,	59	,,
SLOW FREEZING −17°C	15 days −17°C	61	Patent
,,	19 ,, ,,	66	,,
,,	12 ,, ,,	40	Thromb.

* Small aneurysm on graft side of lower anastomosis. Proved due to crack.

† Hæmorrhage from proved crack in graft.

Our present study is concerned chiefly with the effects of varying the freezing gradient and storage temperature. The fact that thrombosis often follows anastomosis of small vessels suggested that the two anastomoses entailed in grafting the carotid arteries of small and medium-sized dogs would provide a stringent test. The abdominal aorta was chosen to represent the larger arteries in which the flow is moderate compared with the flow in the thoracic aorta which formed the subject of an earlier investigation (Hufnagel 1948).

Methods

The carotid arteries and aorta were removed aseptically from dogs killed not more than 4 hours previously, and were then frozen either very rapidly or quite slowly.

As the most rapid freezing agent generally available, liquid nitrogen was employed with and without the use of containers and intermediate cooling agents. *Direct immersion* in liquid nitrogen produced the sharpest fall. Equilibration at −195°C, as evidenced by the cessation of vaporisation, could usually be reached in 10–12 sec. with small vessels and 20–25 sec. with larger ones. When aortas were frozen by direct immersion, cracking sounds were often heard during the last 2 or 3 sec., and these grafts when thawed proved to have fine cracks extending into the lumen. The cracks were usually at the ends of the vessel or near a branch orifice, and some were so fine that stretching of the aorta was necessary to demonstrate them. They were never seen in the smaller vessels, or when the larger grafts were subjected to a two-phase freezing gradient. When the rapid phase was interrupted at 15 sec. and the grafts were then transferred to sterile tubes already at −70°C in the solid carbon dioxide box, very quick freezing could still be obtained without cracking. Since the carotid arteries did not crack, a trial was made of grafts frozen by short or long periods of immersion in liquid nitrogen, the times being 10 or 15 sec. and 5 min. respectively. All grafts were stored in sealed sterile test-tubes in a solid carbon dioxide refrigerator until ready for use.

The slow-frozen group were simply placed in sterile tubes in a standard deep freeze at −15° to −18°C or the freezing chamber of a household refrigerator at −10°C and kept thus until the day of implantation.

Rapid thawing in a large volume of isotonic saline at 37°C was used for the quick-frozen grafts. Those of the slow-frozen group were allowed to come gradually to room-temperature in their storage tubes, being removed from the refrigerator 30 minutes before they were required at the operating-table.

TABLE II—CAROTID HOMOGRAFTS

Method of freezing	Duration and temp. of storage	Period of observation (days)	Result
RAPID FREEZING			
Liq. N₂ 60 sec.	18 days −18°C	27	Patent
,, ,, 5 min.	10 ,, −70°C	67	,,
,, ,, 5 ,,	10 ,, ,,	67	,,
,, ,, 45 sec.	36 ,, −17°C	66	,,
,, ,, 45 ,,	36 ,, ,,	66	,,
,, ,, 5 min.	50 ,, −70°C	126	Thromb.
,, ,, 5 ,,	64 ,, ,,	112	Patent
,, ,, 10 sec.	7 ,, ,,	107	Thromb.
,, ,, 10 ,,	7 ,, ,,	107	,,
,, ,, 5 min.	72 ,, ,,	121	Patent
,, ,, 10 sec.	14 ,, ,,	87	,,
,, ,, 10 ,,	14 ,, ,,	87	Thromb.
,, ,, 10 ,,	21 ,, ,,	111	Patent
,, ,, 10 ,,	21 ,, ,,	111	,,
,, ,, 10 ,,	34 ,, ,,	60	Thromb.
,, ,, 10 ,,	34 ,, ,,	60	,,
,, ,, 20 ,,	44 ,, ,,	86	,,
,, ,, 20 ,,	44 ,, ,,	86	,,
,, ,, 10 ,,	42 ,, ,,	100	Patent
,, ,, 10 ,,	42 ,, ,,	100	,,
,, ,, 15 ,,	42 ,, ,,	87	Thromb.
,, ,, 15 ,,	42 ,, ,,	87	Patent
,, ,, 15 ,,	54 ,, ,,	67	Thromb.
,, ,, 15 ,,	54 ,, ,,	67	,,
,, ,, 45 ,,	183 ,, ,,	44	,,
,, ,, 45 ,,	183 ,, ,,	44	,,
SLOW FREEZING −17°C	29 days −17°C	10	Hæmorrhage
,,	29 ,, ,,	69	,,
,,	30 ,, ,,	66	Thrombosed
,,	30 ,, ,,	66	,,
,,	32 ,, ,,	46	Patent
,,	32 ,, ,,	46	,,

TABLE III—CAROTID HOMOGRAFTS: EFFECT OF VARIATION IN FREEZING METHOD

Time in liquid nitrogen	Result	Time in liquid nitrogen	Result
5 min.	Patent	15 sec.	Thrombosed
5 ,,	,,	15 ,,	Patent
5 ,,	Thrombosed	15 ,,	Thrombosed
5 ,,	Patent	15 ,,	,,
5 ,,	,,		
		10 ,,	,,
60 sec.	Patent	10 ,,	,,
		10 ,,	Patent
45 ,,	,,	10 ,,	Thrombosed
45 ,,	,,	10 ,,	Patent
45 ,,	Thrombosed	10 ,,	,,
45 ,,	,,	10 ,,	Thrombosed
		10 ,,	,,
20 ,,	,,	10 ,,	Patent
20 ,,	,,	10 ,,	,,

TISSUE-CULTURE METHOD

The roller-tube technique was employed (Gey and Gey 1936) with culture medium and treatment of tissues as described by Hanks and Wallace (1949) and Pierce, Gross, et al. (1949), except that we used either 9-day chick embryo or adult dog spleen minced and in 50% extract with balanced salt solution (Hanks) as the growth-promoting portion of the medium. In most of the cultures antibiotics were omitted because we found that they impaired the growth of tissues of low vitality, and even some of the control cultures. Moreover, the medium without them constituted a useful monitor of our aseptic graft-taking technique.

OPERATIVE METHOD

Mongrel dogs averaging 19 kg. in weight were anæsthetised with intravenous sodium pentobarbital.

The abdominal aorta was exposed through a left rectus incision and mobilised between the renal and iliac arteries with division of all branches including the inferior mesenteric at its origin. The aorta was then occluded with cotton-tape tourniquets (Hufnagel 1947 and a segment between them excised. This piece was on the average 2 cm. in length, and the graft which replaced it 3 cm. The graft was sutured in place using continuous everting mattress suture of 5–0 arterial s on atraumatic half-circle needles. Host vessels a grafts were handled only by their adventitia.

Both the carotid operations were usually done at t same time through a midline muscle-retracting incisio since simultaneous carotid occlusion is safe in the d

TABLE IV—FUNCTIONAL RESULTS : ALL GROUPS

Type of graft employed	Total	Patent	Thrombosed	Hæmorrhage
apidly frozen aortic homografts	13	12	0	1
apidly frozen carotid homografts	26	13	13	0
owly frozen aortic homografts ..	3	2	1	0
owly frozen carotid homografts ..	6	2	4*	2*
apidly frozen carotid autografts ..	3	3	0	0
Totals	51	32	16	3

* Includes two cases with both complications.

fter occlusion with rubber-shod serrefines, a segment veraging 2 cm. long would be excised and replaced by a cm. graft. Hæmostasis was usually obtained without he use of *additional sutures. Neither anticoagulant* or antibiotic supporting treatment was employed in ny of these animals.

Results

OPERATIVE INVESTIGATIONS

Macroscopic Observations

All these grafts were studied in the living anæsthetised nimal, immediately before it was killed, after periods of bservation from 27 to 165 days (tables I and II, fig. 12). The majority could be easily dissected free from the surrounding tissues, but where thrombosis had occurred here were dense perivascular adhesions. It was noticed hat before the onset of vasospasm, which developed during manipulation of the vessel, the normal and grafted sections appeared identical. The specimen would then be excised between clamps and opened up at once by longitudinal incision, when the grafted segment assumed an appearance of relative dilation and the whole specimen became shortened (fig. 1). At this stage the adjoining vessel is usually in a state of contraction from the dissection, clamping, and section processes. This correlates with our histological finding that muscle is lost from the media of homografts. Certainly, the phenomenon was not seen in frozen autografts, which contracted in the same way as the normal vessel containing them.

The exposed inner surface of all our specimens showed uniformly satisfactory healing at the anastomoses (fig. 8). Most of the intima was now seen to be quite normal; where irregularity existed its site was generally at the centre of the graft and its extent limited to one part of the circumference (fig. 2). These areas appeared to consist of a slightly roughened thickening of the arterial lining. No example of thrombosis was seen in the quick-frozen aortic series, though one of the slow-frozen abdominal aortic grafts was found to be extensively thrombosed at 40 days. The incidence of failure in the quick-frozen carotid group of experiments was high, so an analysis was made of the circumstances of collection, freezing, storing, and size relationship at operation. Neither the length of storage nor the duration of the postoperative period could be related to the incidence of thrombosis (fig. 12). It was noticed, however, that of the thirteen carotids showing thrombosis, eight came from a single group of vessels collected under circumstances of uncertain asepsis. Of the ten grafts so collected eight became thrombosed after implantation. In the slow-frozen series two developed, on the 10th day, sufficient bleeding to require operation. This complication was not seen in the much larger series of quick-frozen carotid grafts.

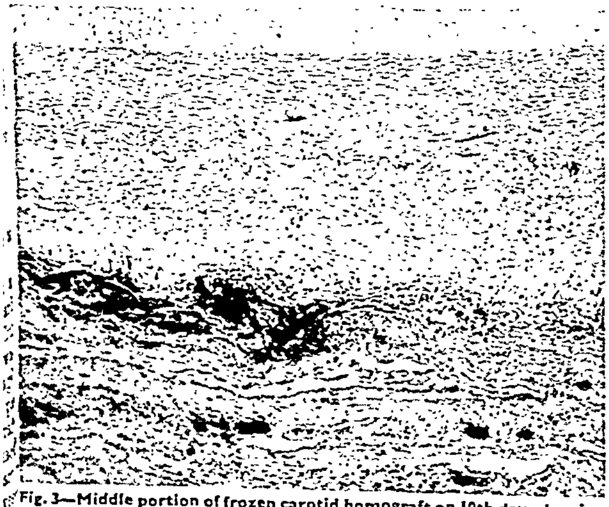

Fig. 3—Middle portion of frozen carotid homograft on 10th day, showing advanced hyalinisation of media, preservation of internal elastic lamina, and newly formed intima from many layers of endothelioid cells.

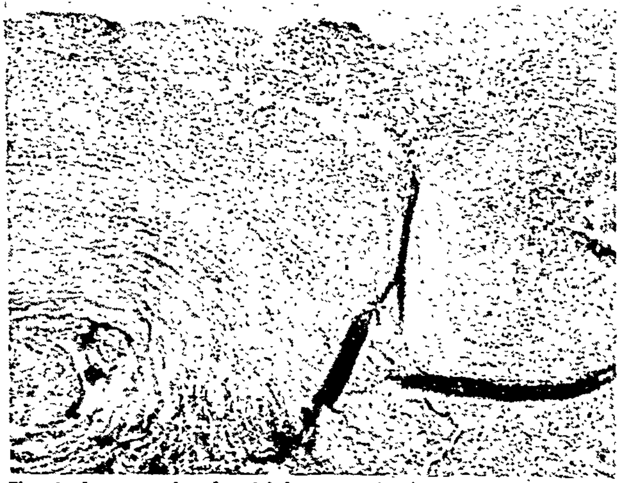

Fig. 4—Anastomosis of quick-frozen abdominal aortic homograft, showing organising thrombus in the intimal groove caused by eversion; also hyalinisation of host media where included in suture.

In the group of rapidly frozen abdominal aortic grafts one animal died from a hæmorrhage on the 10th post-operative day due to a visible longitudinal crack entering the distal suture line. One other animal, when killed on the 100th day, was found to have a small false aneurysm on the graft side of the distal suture line. Both these grafts had been frozen by a method employed early in the experiments in which the graft was directly immersed in liquid nitrogen for 5 minutes. Nearly all the grafts treated in this way showed numerous fine cracks as already described. Only three such grafts were used, and two showed complications attributable to low-temperature cracking. The other had a terminal crack which was discovered and removed before the graft was inserted. Almost all aortic grafts frozen in liquid nitrogen for 5 minutes showed enough cracking to necessitate rejection. However, by the later method of two-phase freezing uniformly satisfactory material was obtained.

Tables I–IV and fig. 12 present case details and an analysis of the whole series.

Histological Examination

Microscopic study of a complex changing process deals with appearances which may be interpreted in different ways. Particularly is this so in the case of homografted tissue, where difficulty arises in distinguishing certain changes of degeneration in the graft, with possible persistence of some groups of donor cells, from regenerative phenomena with invasion of host elements (Eastcott and Hufnagel 1950).

It is well known that water, solutions, and colloids may, in this order of readiness, be solidified by very low temperature in such a way that an amorphous molecular state (vitrification) occurs. A steep thermal gradient minimises the chance of an orderly lattice formation producing crystals. A so-called "dangerous range" of sub-zero temperatures, which varies with the colloid under consideration, must be passed as quickly as possible in both freezing and thawing to enable the change in state to complete its full cycle (Hazel et al. 1949). It seems possible, therefore, that the various recorded examples of tissues of many kinds, from vinegar eels (Luyet and Hodapp 1938) to human spermatozoa (Parkes 1945) surviving very rapid freezing may have passed through such a state. Concentration of the cell colloids by partial dehydration before freezing may favour the development of vitrification. We have tried in various ways to do this but without success. Smith (1950) and Smith and Parkes (1951) have described the use of glycerol-saline for the frozen storage of red cells and ovarian tissue; their results were promising. But survival is quite unpredictable, even with constant technique. This may in part be due to the unreliability of present methods of assessing the viability. We feel that the use of tissue culture as a final criterion is not always reliable in that the cell population surviving may be of insufficient vitality to manifest growth in vitro. Furthermore, the use of this method in a comparative sense is difficult. Even where tissues of likely viability have been used, the inconsistency will not permit statistical interpretation of results. It may be that reimplantation of autogenous tissue after freezing in the manner selected will afford better evidence of survival. This would seem to be true in our experience and that of others (Medawar 1946).

FUNCTIONAL RESULTS

Large Vessels.—In vessels 6 mm. in diameter and larger, rapid freezing can be uniformly relied upon to provide arterial grafts which will remain patent (fig. 8). These vessels show normal physical characteristics and there is no progressive structural change after 3 months. The changes of transplantation, however, are quite variable and an apparently stable state may be reached much sooner. In fifty-three consecutive cases from this and earlier series, no case of thrombosis has been observed in periods up to 4 years. In these the length of the graft seldom exceeded 3 cm. Longer pieces have been shown by McCune and Blades (1951) to function just as well. In the case reported below, a 10 cm. segment was found to be satisfactory, and we have had further clinical experience to confirm this.

Small Vessels.—The cause of the high proportion of failures in this series is difficult to determine. Past experience with simple suture of arteries of 3 mm. and less has shown a much higher incidence of thrombosis than occurs in larger vessels. No comparable work on fresh small vessel grafts is available. It may be significant that eight of the thirteen failures occurred in cases using a suspected batch of grafts. No other definite factor within this group could be demonstrated. The remaining patent carotid grafts showed changes comparable with those described in the aorta and appeared to be similarly well adapted and established (figs. 1 and 2).

Slow-frozen Vessels.—In the small series of slow-frozen grafts with the same operative technique, the complications of hæmorrhage and thrombosis were met with early (tables I and II). The only aortic thrombosis yet encountered was in this group. The carotid series was too small for statistical evaluation of the incidence of thrombosis. Hæmorrhage occurred twice in this small series but not in the rapidly frozen group. It would seem that slow freezing is both functionally and histologically less satisfactory than the rapid technique which we have employed.

METHOD OF CHOICE FOR FROZEN GRAFTS

We have been impressed with the possibility of maintaining life at low temperatures. The accumulated evidence of earlier work on preservation by rapid freezing leads to the conclusion that in this respect alone the method offers much more promise than any other for the supply of fresh, readily available material in adequate quantities after prolonged storage. The principles to be observed in preparing frozen arterial grafts should be:

1. Freezing by the steepest available gradient:

(*a*) If liquid nitrogen is used for initial freezing, a two-phase method is necessary with interruption at 15 sec. as described above.

(*b*) Solid carbon dioxide ether mixture offers a reliable freezing method without the need for interruption. Cell survival is less likely than with (*a*).

2. Storage at the coldest practical level:

(*a*) Choice of storage temperature usually lies between that of an electrical deep-freeze appliance at −15° to −20°C, or

(*b*) More effective but less convenient, the solid carbon dioxide bank at −70°C.

Case-report

A man aged 60, a milk roundsman, was walking up a steep hill in July, 1951, when he experienced a pain in the left calf. This recurred on level walking farther than 100 yards, and would take 2–3 minutes' rest to pass off. A week later he noticed numbness and tingling of the left foot which also became "cold and lifeless," particularly when he was in bed. Two weeks after the first attack of claudication he noticed swelling of the left foot. When seen at St. George's Hospital, London, on Aug. 1, 1951, he had œdema of both ankles, extending to the knee on the left side. The swelling quickly resolved with bed rest in hospital. At this stage his limit of walking was 50 yards. None of the pulses in this leg were palpable except over the upper part of the femoral.

Examination (St. Mary's Hospital, Oct. 6, 1951)

General condition good; spare physique; no abnormal signs in heart and chest examination except for moderate emphysema. Blood-pressure 190/90. Radial artery thickened. Right leg: pulses all present; no œdema. Left leg: femoral pulse only; slight œdema of left foot, which was slightly warmer than the right.

Investigations

Plain radiography of both legs: no arterial calcification seen. Bilateral femoral arteriography by Mr. V. G. Walker at St. George's Hospital: both systems showed fairly advanced patchy arteriosclerotic narrowing and on the left side there was a complete block in the popliteal artery approximately 8 cm. long with its lower limit just above the femoral condyles. There appeared to be a good collateral circulation (fig. 9).

Operation (Oct. 10, 1951)

Endotracheal anæsthesia (Dr. C. A. Cheatle). Prone position. Longitudinal posterior exposure of the popliteal fossa. The medial popliteal nerve being dissected free and retracted laterally, two small muscular branches were divided in order to expose the underlying artery. At the joint level the arterial lumen could be felt but did not pulsate. Above this the artery was cord-like (fig. 11) and adherent up to just below the adductor opening where a strong pulsation could be felt. A short length above and below the block was mobilised to permit the application of Blalock's clamps; collaterals were preserved by placing small bulldog clamps upon them. The blocked segment measuring 10 cm. was excised.

A frozen graft of the appropriate size was brought from the bank and was thawed at the operating-table by immersing it in isotonic saline at 41°C. The graft was then sutured into place, using 00000 arterial silk on a small curved non-cutting needle, with the normal eye. The ends of the host artery were in some places much thickened, but the intima could be identified and an everting suture performed. On removal of the clamps, pulsation was seen in the graft, and the left salis pedis pulse could be felt for the first time. Hæmostasis the upper anastomosis required one additional suture; lower anastomosis did not leak. The wound was closed h drainage, because it was decided that with a diseased t vessel heparin would be advisable, and 12,500 units were en intravenously at the end of the operation.

ogress

The pulses in the left foot have remained since. The foot elf became hot and sweated normally. A second and last se of heparin was given 6 hours after operation. By the th day the patient was walking. Arteriography was per-med (fig. 10) on the 14th day and showed that the graft d, the named vessels peripheral to it were functioning. ve months after operation the pulses in the left foot are sily palpable. He is able to walk and run without audication and has returned to work.

Summary

1. A method of rapid freezing for arterial homografts described.

2. Material of this kind has been employed in 42 perations in the carotid artery and abdominal aorta of ie dog.

3. Cell survival after such rapid freezing has been iown to be possible.

4. These grafts function as well as fresh tissue and ffer the advantages of ready availability in wide selection ver long periods of storage.

5. A case is described in which an occluded popliteal rtery was restored using a quick-frozen arterial omograft.

This investigation was supported by grants from the National Ieart Institute of the United States National Institutes of Iealth, and from the Eugene Higgins Fund, and by an institu-ional grant from the National Cancer Society.

Our thanks are due to Mr. Victor Riddell and Mr. A. H. M. Siddons for referring the patient whose case is described, and o Miss P. Allison for the radiographs.

REFERENCES

Bensley, R. R., Gersch, I. (1933) *Anat. Rec.* 57, 205.
Birdseye, C. (1929) *Industr. Engng Chem.* 21, 414.
Blakemore, A. H., Lord, J. W. (1945) *J. Amer. med. Ass.* 127, 685.
Carrel, A. (1908) *Ibid,* 51, 1662.
— (1910) *J. exp. Med.* 12, 460.
— (1912) *J. Amer. med. Ass.* 59, 523.
Deterling, R. A. jun., Coleman, C. C., Parshley, M. S. (1951) *Surgery,* 29, 419.
Eastcott, H. H. G., Hufnagel, C. A. (1950) *Surg. Forum Amer. Coll. Surg.* Philadelphia.
Garber, L. Z., Bush, L. F. (1950) The Bone Bank and the Use of Homologous Bone. Monographs on Surgery. New York.
Gey, G. O., Gey, M. K. (1936) *Amer. J. Cancer,* 27, 45.
Gross, R. E., Bill, A. H., Pierce, E. C. (1949) *Surg. Gynec. Obstet.* 88, 689.
Guthrie, C. C. (1912) Blood Vessel Surgery and its Applications, London and New York.
Hanks, J. H., Wallace, R. E. (1949) *Proc. Soc. exp. Biol., N.Y.* 71, 196.
Hazel, F., Parker, J. A., Schipper, E. (1949) *Science,* 110, 161.
Hufnagel, C. A. (1947) Clinical Congress of the American College of Surgeons.
— (1948) *Ibid.*
Katzin, H. M. (1947) *Amer. J. Ophthal.* 30, 1128.
Keith, W. S. (1934) *J. Bone Jt Surg.* 16, 314.
Loeb, L. (1930) *Physiol. Rev.* 10, 547.
Luyet, B. J., Gehenio, P. M. (1940) *Biodynamica,* 48, 2.
— Hodapp, E. (1938) *Proc. Soc. exp. Biol., N.Y.* 39, 433.
McCune, W. S., Blades, B. (1951) *Ann. Surg.* 134, 769
Medawar, P. B. (1946) *Brit. J. exp. Path.* 27, 9.
Mider, G. B., Morton, J. J. (1939) *Amer. J. Cancer,* 35, 502.
Parkes, A. S. (1945) *Brit. med. J.* ii, 212.
Pierce, E. C., Gross, R. E., Bill, A. H., Merrill, K. E. (1949) *Ann. Surg.* 129, 333.
— Rheinlander, H. F., Moritz, A. R., Gross, R. E., Merrill, K. E. (1949) *Amer. J. Surg.* 78, 314.
Smith, A. U. (1950) *Lancet,* ii, 910.
— Parkes, A. S. (1951) *Ibid,* ii, 570.
Strumia, M. M., Hodge, C. C. (1945) *Ann. Surg.* 121, 860.
Swan, H., Robertson, H. T., Johnson, E. J. (1950), *Surg. Gynec. Obstet.* 90, 568.
Webster, J. P. (1944) *Trans. Amer. Surg. Ass.* 62, 431.
Weiser, R. S., Osterud, C. M. (1945) *J. Bact.* 50, 413.
Weiss, P., Taylor, A. C. (1943) *Proc. Soc. exp. Biol., N.Y.* 52,

CONGENITAL ANOMALIES OF THE AORTIC ARCH

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With illustrations on plate

Although Hunand is claimed to have first described, in 1735, a right subclavian artery passing behind the œsophagus, precedence is usually given to Bayford (1789), who gave a precise account of the necropsy findings in a woman who died of inanition in her 61st year. She had suffered since infancy from dysphagia and a sense of suffocation, and necropsy showed a normally placed aortic arch, but the right subclavian artery arose from the distal left side of the arch and passed behind the œsophagus upwards to the right to reach its normal position. Bayford dubbed this a case of dysphagia lusoria; for in his day it was popular to describe a minor congenital anomaly as a *lusus naturæ,* a prank or trick of Nature.

Gross (1945), of Boston, claimed the first reported division of a double aortic arch with complete relief of the infant's symptoms. Since then Gross and Neuhauser (1951) have reported 40 cases treated surgically. These and other published reports (Wolman 1939, Neuhauser 1946, Gross and Ware 1946, Gross and Neuhauser 1948) have led to more general recognition of the clinical picture produced by congenital abnormalities in the aortic arch and its branches. These abnormalities are probably more common than the scanty literature suggests.

EMBRYOLOGY

A pair of tubular vessels, the primitive aortæ, are the first to form, running backwards one on each side of the notochord, and passing backwards into the body stalk, along which they are carried as the umbilical arteries. The forward growth and flexure of the head cause the anterior portions of the primitive aortæ to be folded forward and lie on the ventral aspect of the foregut; there are now, on each side, a dorsal aorta and a ventral aorta united by the two curved portions; these latter are the first aortic arches. Five further arches are subsequently formed, corresponding to the branchial arches, the earlier anterior ones mainly disappearing as the later ones develop.

About the third week the paired dorsal aortæ fuse from about the level of the fourth dorsal vertebra to form the definitive descending aorta. The caudal ends of the ventral aortæ also fuse, to form the single tubular heart, which elongates and bends into an S-shaped loop, the anterior part convex ventrally and to the right, and the posterior convex dorsally and to the left. The anterior part forms the primitive ventricle, the bulbus cordis, and the truncus arteriosus. The last named develops within it the spiral aortopulmonary septum, which divides the vessel into ascending aorta and pulmonary artery and, rotating through three-quarters of a circle, causes the pulmonary artery, arising anteriorly and to the right, to pass to the left of the aorta and finally to lie on the dorsal side of the aorta before its division into right and left branches. The aortopulmonary valve finally terminates headwards just dorsal to the sixth aortic arches, closing these off from the aorta proper, so that the right and left pulmonary arteries are formed by these sixth arches.

Fate of the Arches

The first and second arches completely disappear at an early stage (fig. 1). The third arches form the common carotid artery on each side. The right fourth arch persists normally as the right subclavian, whereas the left fourth arch gives rise to the arch of the aorta as far as the termination of the ductus arteriosus, where it is joined by the transient fifth arch, which also disappears (but see description of case below). The ventral portions of the sixth arches remain as

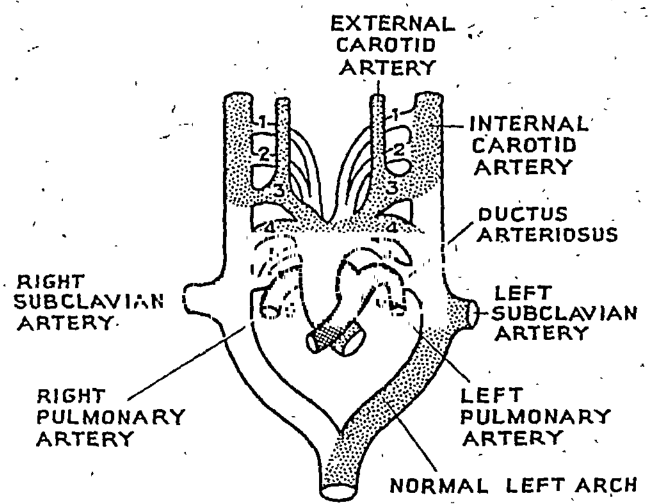

Fig. 1—Fate of arches.

the right and left pulmonary arteries, but the distal portion on the left side becomes the ductus arteriosus, below which the left dorsal aorta persists as the descending aorta, the right dorsal aorta disappearing.

CLASSIFICATION

A comprehensive classification based on a functioning double aortic arch has been worked out by Edwards (1948). Although, on first inspection, it is forbidding in its detail it gives a very clear explanation. Neuhauser (1946) has made a simpler classification, which though not based on the essential anomaly of the persistent right fourth aortic arch, is more convenient:

I. *Situs Inversus Viscerum*

II. *Right Aortic Arch without Inversion*

(1) *Anterior Type.*—Aortic arch, anterior to trachea, passes over right bronchus, and descending aorta lies on right side.

(2) *Posterior Type.*—Aorta passes over right bronchus, then to left behind œsophagus, and descending aorta courses to right of normal left-sided distribution:

- (*a*) Right aortic arch in which left subclavian artery arises last from arch and crosses behind œsophagus to its distribution.
- (*b*) Right aortic arch in which no vessel arising from arch crosses midline behind œsophagus.
- (*c*) Right aortic arch with persistent left aortic diverticulum, which gives origin to left subclavian artery. Aortic diverticulum represents posterior portion of left aortic arch which would normally give rise to left subclavian. No vessel from arch crosses midline posteriorly.

III. *Double Aortic Arch*

- (*a*) Both aortic limbs patent, anterior limb being usually smaller than posterior.
- (*b*) One aortic limb obliterated.

IV. *Anomalous Right Subclavian Artery*

Arises last from normal left aortic arch and crosses midline to its distribution on right side. Right portion of double arch has disappeared between origins of right common carotid and right subclavian arteries, so that last-named arises from left aortic arch where right arch would have joined it. Holzapfel (1899) found the artery lying behind the œsophagus in 107 cases, between the trachea and the œsophagus in 20, and in front of the trachea in 6.

V. *Patent Ductus Arteriosus*

VI. *Coarctation of Aorta*

Posterior type of right aortic arch and double arch are often associated with ductus arteriosus from pulmonary artery, thus forming a complete vascular ring.

CLINICAL PICTURE

In most cases there are no symptoms. Where these are present they occur either in early infancy or late in adult life. After childhood the vessels lengthen, thus relieving the pressure on the trachea and œsophagus, but degenerative changes in the vessel walls may produce symptoms after middle age. According to the type of vascular anomaly present pressure may be exerted on the trachea or the œsophagus, or both.

Tracheal Obstruction

Wheezy or crowing respiration is usually noticed soon after birth, and is worse during feeding, which often is punctuated by "rests" while the infant regains its breath. The baby often keeps its head overextended, a position which stretches and straightens the trachea. In Gross and Neuhauser's (1948) case the child lay habitually in opisthotonus with fully extended head. Owing to the partial tracheal obstruction, suprasternal and intercostal retraction of the soft parts may be observed with inspiration. Recurrent infection of the respiratory tract occurs owing to the obstruction and to inhalation of regurgitated food, and may occasion death.

Œsophageal Obstruction

As an infant's food is at first entirely liquid, dysphagia is rarely so early or so severe a symptom as the respiratory difficulty. There may be slowness in feeding or inability to take a full feed. When the infant begins to take solid food, the dysphagia becomes more obvious, and can lead to malnutrition.

Radiology

The diagnosis cannot be made without adequate radiological investigation. Apart from the possible associated pneumonitis, a straight anteroposterior film will show the trachea to be narrowed bilaterally in its lower portion if a double aortic arch is present. A similar appearance is presented when a right arch and a left ductus arteriosus complete the vascular ring. Lateral films demonstrate the indentation of the anterior tracheal wall by an anterior arch, or a longer more oblique defect caused by an abnormal left common carotid or an innominate artery. A clearer picture can be made by intratracheal instillation of a few millilitres of iodised oil; but in view of the partial tracheal obstruction and recurrent pneumonitis, it is safer to rely on good-quality straight films.

A barium swallow in cases of double aortic arch shows a large rounded indentation of the posterior and right lateral walls of the œsophagus at the level of the third or fourth dorsal vertebra. A similar appearance is found in right posterior arch with left ductus arteriosus. The classical dysphagia lusoria, from aberrant right subclavian artery, in its common posterior position, is demonstrated by an oblique indentation of the posterior œsophageal wall running, from below and the left, upwards and to the right. A simple right aortic arch with right descending aorta pushes the œsophagus to the left.

Angiocardiography can give precise information about the presence of double aortic arch and the origins of the major arteries, and was of great assistance in the present case.

TREATMENT

Where the symptoms are mild, there is no indication for surgery, because usually the obstruction abates after the first few years of life (Apley 1949). Unfortunately a considerable proportion of these small patients are in mortal danger from pulmonary infection. In these surgery should be undertaken as soon as the pneumonitis has been controlled with antibiotics.

An excellent exposure is given by the standard posterolateral thoracic incision used in this country, though in American reports the more favoured anterolateral approach has been used. The posterior attack has the advantage that the retro-œsophageal vessel can e dealt with more easily. The thymus gland overlies he major vessels and must either be removed, as ecommended by Gross, or partially dissected away and eld forward as in the present case. In double aortic rch the anterior limb is usually the smaller and can herefore be divided, preferably between the origins of he left common carotid and left subclavian arteries. his preserves an adequate blood-flow into the left ommon carotid, and causes the proximal remnant of he anterior arch to move upwards and release its onstriction of the trachea. If the common carotid rtery still seems to press upon the trachea, a few fine titches can be placed through its adventitia, and hrough the back or substance of the sternum, to hold the vessel forward (Gross and Neuhauser 1951). An aberrant nnominate artery can be similarly treated.

The ductus should always be divided, especially where a right posterior arch is pulled forward by the left ductus. An aberrant right subclavian artery can be divided without endangering the blood-supply of the arm.

The subsequent postoperative course of these patients should be entirely uneventful, and the cessation of symptoms complete. Gross and Neuhauser (1951) recorded 40 cases treated surgically, with 4 deaths and 36 cures; all the deaths took place in cases of double aortic arch, where the clinical picture is more severe and the operation more difficult.

CASE-RECORD

A girl, aged 2 years, is the second child of her family; the elder, aged 8, is healthy. The parents have had no illnesses of importance, and there are no known examples of congenital defect in other members of the family. Born at term, after a normal pregnancy and labour, she weighed $8^1/_2$ lb. From birth she was artificially fed on dried milk, which was taken well, and her weight increased satisfactorily. Her developmental milestones were passed at the customary ages.

Stridor was noticed from the time of birth and was observed by the midwife. From an early age the patient was subject to frequent respiratory infections, and at the age of 1 year her chest was radiographed and bronchial asthma was diagnosed. During her second year cough and wheezing became progressively worse, especially after an attack of measles, from which time the cough was reported to resemble that of whooping-cough.

Dysphagia was noticed at about 6 months when she began to take solid food. The food seemed to stick in the gullet without causing much distress, until a piece of apple became lodged and could not be moved. She was extremely distressed and collapsed, and was admitted to a local hospital, where laryngoscopy showed no abnormality. Presumably the food was dislodged on the way to hospital, and she was discharged apparently normal next day. After this episode dysphagia persisted in a rather periodic fashion, but tended, on the whole, to become worse. The parents had to invert her when particles of food became impacted.

Examination

She was a rather fat, unhappy, red-faced child with a short neck, and she weighed $31^1/_2$ lb. Severe inspiratory and expiratory stridor was heard with a frequent wheezing cough. She did not tend to hyperextend her head. Her heart was not enlarged, and the heart sounds were pure. Her blood-pressure was 110/80 mm. Hg in both arms, and her femoral pulses were strong. Diffuse râles with bronchial spasm were heard in the lungs. Nothing else of importance was found elsewhere.

Investigation and Diagnosis

Radiography of the chest showed normal lung fields, probable right-sided aortic arch, and trachea apparently slightly narrowed in lateral view.

Barium swallow (fig. 2) showed constriction of the œsophagus at the level of the fourth thoracic vertebra. In the first oblique position there was a posterior indentation of the œsophagus at this site.

Angiocardiography (fig. 3).—The 5-sec. film showed filling of a normal left ventricle and a right-sided aortic arch. A large posterior aortic arch could be followed down into the descending aorta, and a small anterior aortic arch was visible giving rise to a left common carotid and left subclavian arteries.

Diagnosis.—The findings showed that the patient had a double aortic arch, which falls into Neuhauser's category IIIa (see above). While she was under observation in hospital the stridor and cough persisted, although dysphagia was slight, because little solid food was given in view of the alarming reports of the parents. Despite the fact that she was 2 years old there had been no lessening of the symptoms; indeed her parents said she was becoming worse. Operation was therefore considered advisable.

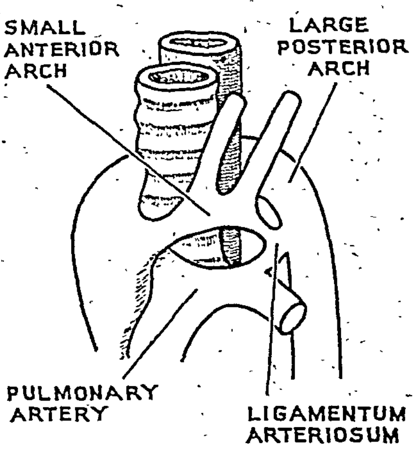

Fig. 4—Positions of great vessels found at operation (innominate artery not shown).

Operation (Oct. 10, 1951)

Left posterolateral thoracotomy through the 5th rib bed exposed a large thymus gland over the anterior aspect of the great vessels; this was freed and retracted forwards. A complete right posterior arch was present; the smaller anterior arch gave rise to the left common carotid and subclavian arteries, and then, much diminished in size, joined the aortic end of the ligamentum arteriosum (fig. 4). This small segment was divided between clamps, and the ends were closed with arterial sutures; the ligamentum arteriosum was then also divided, a ligature and transfixion suture being applied to each end. The trachea and œsophagus were seen to be completely freed from encircling compression, and the wound was closed without drainage.

Convalescence

Recovery from operation was uneventful. Stridor was no longer present, and signs were no longer detected in the lungs. Dysphagia disappeared. Radiography in the first oblique position after a barium swallow naturally showed only slight lessening of the posterior indentation of the œsophagus, although severance of the vascular ring allowed the barium to pass the constricted area more readily.

SUMMARY AND CONCLUSIONS

An account is given of the various congenital anomalies of the aortic arch and its major branches. The embryology is described, showing how the variations from the normal arise. The clinical picture that results from partial tracheal and/or œsophageal obstruction in infancy is portrayed, together with the radiological findings.

Where the clinical condition is serious, surgery is indicated, and the operations are straightforward and highly successful.

A case exemplifying the classical picture is described, and after operation the child is completely well.

We have not found any published report of a similar case undergoing surgery in this country, but the condition cannot be excessively rare. If it is kept in mind as a cause of stridor, recurrent pulmonary infection, and dysphagia in infancy, probably many more cases will be recognised, and surgery applied if warranted.

We warmly thank Dr. A. P. Booth, director of radiology, Royal Hospital, Wolverhampton, for his interpretation of the radiographs and angiograms; Dr. J. F. Rickards, the anæsthetist; and Mr. D. Paton, of the hospital photographic department, who made a colour film of the operation, and has produced the photographs. The patient was shown in a clinical meeting of the pædiatric section of the Royal Society of Medicine, and we are grateful to the editorial committee of the Society for permission to publish.

References overleaf

PULMONARY HÆMOSIDEROSIS

REPORT OF A CASE

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With illustrations on plate

RECENT articles by Lendrum, Scott and Park (1950) and Ellman and Gee (1951) have recorded their observations on the secondary effects of cardiac disease on the lungs. We have been studying a case of pulmonary hæmosiderosis and mitral stenosis which is of particular interest in that the patient remains comparatively well and continues to perform his normal work, yet the definite radiological development of pulmonary changes due to circulatory back-pressure has been observed over a period of three years.

CASE-REPORT

We first saw the patient at a routine medical examination in September, 1947. He was then 22 years of age and he had just completed three years' service as a stoker in the Royal Navy. He gave no history of serious illness and his parents and he have since asserted quite definitely that he has never had rheumatic fever or chorea. Although an occasional apical systolic murmur was heard at this examination, he was accepted for employment. In July, 1948, he was found to have a definite apical presystolic murmur but his exercise tolerance was regarded as normal and he was, in fact, managing fairly heavy manual work perfectly well. Soon after this examination he was admitted to hospital complaining of shortness of breath on exertion. Apparently no cardiac lesion was discovered while he was in hospital and the X-ray appearances of his lungs in August and November, 1948, were considered normal. The diagnosis was "anæmia and general debility."

On discharge from hospital he resumed work and remained well until March, 1949, when he coughed up a small quantity of blood and noticed that he was again somewhat breathless on exertion. He looked pale and ill and the presystolic murmur was still present. Radiography of his chest now showed the bilateral middle zone opacities of pulmonary œdema (fig. 1). A blood examination showed an orthochromic anæmia with a hæmoglobin value of 45%. The Wassermann reaction was negative.

He was re-examined in November, 1949, having been absent from work for six months. He felt perfectly fit, had no cough, and was not breathless, even on exertion. Radiography, however, showed mottling of both lung fields excluding the apices, and some fluid in the left pleural space seeping into the interlobar fissure (fig. 2). We suggest that these radiological appearances represent further steps in the pathological effects of chronic back-pressure in the pulmonary circulation: they are early evidence of the deposition of iron pigment in the œdematous lung and the transudation of fluid into the pleural cavity.

Except for a period of one month off work after a slight hæmoptysis in May, 1950, he remained well and continued work as a storekeeper until he was again examined in March, 1951. At that time he felt fairly well but was occasionally short of breath. The presystolic murmur was still present and the blood-pressure was 106/64 mm. Hg. X-ray examination on this occasion showed hæmosiderosis affecting all areas, except the apices, of both lungs and, in addition, the presence of fluid in the right pleural space (fig. 3).

In April, 1951, he had another slight hæmoptysis, consisting of blood-streaked sputum, and he rested at home for three weeks. On resuming work in May, he stated that although he was certainly breathless as a result of any excessive exertion, such as running a short distance for a bus, he felt perfectly well. He looked pale but not ill. A well-marked apical presystolic murmur was still present and the pulmonary second sound was greatly accentuated. The blood-pressure was 125/80. A few added moist sounds and slight dullness were present at both bases and pulmonary arterial pulsation was audible over both lungs. There was no œdema of the ankles. Radiography of the chest showed no extension of the hæmosiderosis, but fluid was now present in both pleural cavities.

The combination of frequent small hæmoptyses, dyspnœa on exertion, a persistent apical presystolic murmur and the radiographic appearance of pulmonary œdema leave little doubt that this patient suffers from mitral stenosis, which we regard as the basic cause of the various radiological changes described.

DISCUSSION

This case is an example of a mitral stenosis compensated, at least temporarily, by a right ventricular hypertrophy, but only at the expense of raising the blood-pressure in the pulmonary arteries above the pressure in the bronchial arteries. Lendrum et al. (1950) point out that this must lead, sooner or later, to hæmorrhage from the bronchopulmonary anastomoses, sometimes sufficient to produce hæmoptysis. They attribute hæmosiderosis occurring in mitral stenosis to multiple small hæmorrhages, most of which do not produce frank blood in the sputum.

On the other hand, Kerley (1951) thinks that hæmosiderin is deposited in the lungs because it is insoluble in the alkaline medium of the œdematous lung. This means that pulmonary œdema must precede the appearance of hæmosiderin in the lung. Doig and McLaughlin (1948) have shown that the radiological changes in welders' siderosis may disappear. This is presumably because the inorganic iron causing this disease is removed by phagocytosis. The nodules of pulmonary hæmosiderosis have little, if any, tendency to resolve (Prendergrass et al. 1949); so presumably, the phagocytes are unable to remove the iron. Indeed, as Ellman and Gee point out, the condition would not occur at all if phagocytosis were effective. The same authors quote the work of Strassman (1944) which showed that, in a normal rabbit lung, phagocytosis of injected red cells was effective and rapid; but, in the presence of pulmonary œdema, phagocytosis was much delayed. They go on to quote the suggestion of Gumpert (1947) that "œdema and venous congestion cause some obstruction to the normal lymphatic drainage of the alveolar histiocytes responsible for the removal of intra-alveolar red cells."

We were interested in this case because the X-ray films showed the presence of pulmonary œdema before the nodular shadows of hæmosiderosis appeared. This is in keeping with the pathological sequence suggested by Ellman and Gee. The case also gives some indication of the time taken for pulmonary hæmosiderosis to become apparent radiologically. Thus, this patient was said to have a normal chest radiograph in November, 1948. In March, 1949, the appearance was that of pulmonary œdema and some eight months later there was evidence of early pulmonary hæmosiderosis. After a further sixteen months, the changes were those typical of hæmosiderosis.

We wish to express our thanks to Dr. Andrew Meiklejohn for his advice and to the South Eastern Gas Board for permission to publish this case.

REFERENCES

Doig, A. T., McLaughlin, A. I. G. (1948) *Lancet*, i, 789.
Ellman, P., Gee, A. (1951) *Brit. med. J.* ii, 384.
Gumpert, T. E. (1947) *Ibid*, ii, 488.
Kerley, P. (1951). *In* Shanks and Kerley's Textbook of X-ray Diagnosis. London; vol. ii, p. 179.
Lendrum, A. C., Scott, L. D. W., Park, S. D. S. (1950) *Quart. J. Med.* 19, 249.
Prendergrass, E. P., Lane, E. L., Ostrum, H. W. (1949) *Amer. J. Roentgenol.* 61, 443.
Strassman, G. (1944) *Arch. Path.* 38, 76.

MR. DOLTON, DR. EVERLEY JONES: REFERENCES

Apley, J. (1949) *Proc. R. Soc. Med.* 42, 918.
Bayford, D. (1789) *Mem. med. Soc. Lond.* 2, 271.
Edwards, J. E. (1948) Cited by Brown, J. W. (1950) Congenital Heart Disease. 2nd ed., London.
Gross, R. E. (1945) *New Engl. J. Med.* 233, 586.
— Neuhauser, E. B. D. (1948) *Amer. J. Dis. Child.* 75, 570.
— — (1951) *Pediatrics*, 7, 69.
— Ware, P. F. (1946) *Surg. Gynec. Obstet.* 83, 435.
Holzapfel, G. (1899) *Anat. Hefte.* 12, 369.
Hunauld (1735) Cited by Gross, R. E., Ware, P. F. (1946) *Surg. Gynec. Obstet.* 83, 435.
Neuhauser, E. B. D. (1946) *Amer. J. Roentgenol.* 56, 1.
Wolman, I. J. (1939) *J. Pediat.* 14, 527.

LOCAL USE OF CHLORAMPHENICOL IN WOUND INFECTIONS

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FEW reports have been made of the local application of chloramphenicol ('Chloromycetin') in infected wounds. Altemeier and Culbertson (1951), in an extensive review of the use of chloramphenicol in surgery, do not even mention its local use.

Coppleson (1951) reports two cases of anaerobic wound infection which did not respond to systemic antibiotics, including chloramphenicol, but cleared dramatically after the local application of chloramphenicol.

Gilles (1951) reports a case of typhoid osteitis with a persistent discharging sinus that resisted local surgical attack and two courses of systemic chloramphenicol but healed soundly within fifteen days' treatment with local chloramphenicol powder 0·25 g. daily.

Lewis and Gray (1951a and b) describe the use of local chloramphenicol in chronic suppurative otitis media. Since chloramphenicol is only slightly soluble in water or in saline solution, a 15% solution of chloramphenicol in propylene glycol was made, and wicks soaked in it were loosely packed into the chronically infected cavities. Such wicks were still sterile after forty-eight hours in situ and retained sufficient chloramphenicol to produce a large zone of inbition to bacterial growth when placed on a plate inoculated with *Shigella sonnei* and *Bact. coli*. Lewis and Gray were so impressed with the results of local chloramphenicol in otology that they suggested its use in a larger field.

TABLE I—ANALYSIS OF CASES

Type of application	No. of cases	Days to obtain first negative swab	Minimal and maximal times to obtain first neg. swab	Average time for all methods and organisms
5% chloramphenicol in propylene glycol	10	2–3 days	12 hr.–5 days	4–5 days
5% chloramphenicol in lactose	14	4 days	12 hr.–8 days	
A combination of both types	6	7 days	3–21 days	

Magauran (1951) cites his experiences with topical chloramphenicol in other branches of ear, nose, and throat surgery; he used it combined with a bland dusting powder to reduce the tendency to local allergic reactions.

Chloramphenicol has also been used topically in penicillin-resistant staphylococcal meningitis, where its introduction into the cerebrospinal fluid was of great value (Anderson and Ellis 1951); in ophthalmology (Leopold 1951, Magnol 1950); and in dermatology (Alderson 1951, Newman and Feldman 1951).

Seltzer and Bender (1950a and b) showed that a chloramphenicol-streptomycin combination in propylene glycol would sterilise 80% of dental root infections, the remaining 20% being due to infection with *Candida albicans*.

Penicillin and sulphonamide have been used locally for years (Clark et al. 1943); but, since most of the organisms now infecting wounds in civilian practice have become resistant, or were never sensitive, to penicillin therapy, the use of penicillin is somewhat limited, and streptomycin has been used instead with a good measure of success. Wilson (1948) used streptomycin in infected wounds, and Kilner et al. (1951) report encouraging results from the application of streptomycin to infected wounds before grafting. We also have used streptomycin in this way with similar results. Its use, however, has now been discontinued because it often rapidly produces resistant strains of organisms (Garrod 1951), particularly of *Staph. aureus*, *Pseudomonas pyocyanea*, and *Proteus vulgaris*. Furthermore, since streptomycin is one of the few effective drugs in the treatment of tuberculosis, we feel that its use should be restricted to cases in which there is no alternative treatment.

The treatment of penicillin-resistant wound infection was carried a stage further by Jackson et al. (1951), who report on the use of local polymyxin E ('Aerosporin') in *Ps. pyocyanea* infections in burns. They found that this antibiotic was effective against *Ps. pyocyanea* when used in even small concentration, and the healing-time of burns with full-thickness skin loss was appreciably reduced. On the other hand, polymyxin has little or no demonstrable effect on *Staph. aureus*, *Strep. hæmolyticus*, *Proteus vulgaris*, and some coliforms.

We have found that local chloramphenicol is active not only against *Ps. pyocyanea* but also against *Strep. hæmolyticus*, *Proteus vulgaris*, coliforms, and penicillin-resistant *Staph. aureus*. It is now the exception for us to find a strain of *Staph. aureus* which is susceptible to either penicillin or streptomycin. Garrod (1951) has discussed this matter of acquired resistance to chemotherapeutic agents, and states that there is reason to believe that the resistance of the organisms to chloramphenicol is "slow to develop, moderate in degree, and not necessarily permanent." Altemeier and Culbertson (1951) also mention the slower rate of development of resistance.

At present chloramphenicol seems to be the most useful and powerful antibiotic for the treatment of wound infections, with a wide range of activity against the viruses and both gram-positive and gram-negative bacteria. It is particularly useful against those very organisms, the gram-negative bacilli and the penicillinase-producing staphylococci, that constitute the main flora of infected wounds. Pulaski (1951) states that more than 90% of the common organisms encountered in surgery are susceptible to chloramphenicol.

PRESENT INVESTIGATION

Thirty consecutive cases of wound infection, including infected burns, gravitational ulcers, pedicle flaps, grafts, and abscess cavities, were treated with chloramphenicol locally.

Owing to the varied nature of the lesions both dry and moist applications were used. In many of the cases a powder of 5% chloramphenicol in lactose was used, but where a moist application was more suitable a solution of 5% chloramphenicol in propylene glycol was used. This solution was either irrigated into the cavities or applied on wicks or gauze packs.

TABLE II—ORGANISMS FOUND ON INITIAL CULTURE WITH CLEARANCE TIMES

Organism	Total no. of cases	No. of cases with pure flora	Average clearance time (days) with chloramphenicol in		No. of cases with other organisms	Average clearance time (days) when occurring with other organisms	Sensitivity to	
			Propylene glycol	Lactose			Chloramphenicol	Propylene glycol
Staph. aureus	21	13	2	6	8	3	2·5%	Nil
Ps. pyocyanea	10	5	2–3	5	5	3	2·5% (5% in 1 case)	Nil
Strep. hæm. B	3	—	—	—	3	1	2·5%	Nil
Proteus vulgaris	3	2	3–4	—	1	2	2·5%	Nil
Coliform	5	—	—	—	5	3–4	2·5%	Nil
Mixed	11	—	—	—	11	3	2·5%	Nil

Twenty-eight of these cases had previously been treated with little or no success by alternative local measures and systemic chemotherapy, twenty having received courses of penicillin, aureomycin, or chloramphenicol systemically. Since there had been so great an improvement in the lesions treated with local chloramphenicol, it was not considered necessary, for the purposes of a pilot investigation, to use controls.

ROUTINE TREATMENT

Those lesions which appeared to be infected were initially swabbed. This generally showed that an infection was present and was usually caused by penicillin-resistant organisms (table II). Next day, when the preliminary bacteriological report had been received, another swab was taken, the area was cleaned with saline solution and dried, and chloramphenicol was applied locally as either a powder or a solution.

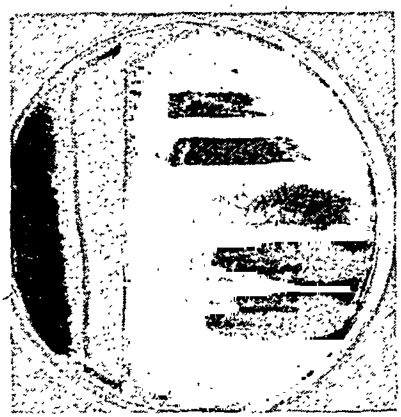
Fig. 1—Gutter sensitivity test showing zone of inhibition produced by 2·5% chloramphenicol on two strains of penicillin-resistant staphylococci (upper) and three strains of *Ps. pyocyanea* after overnight incubation.

In the earlier cases we generally used the powder, applying the solution only in cavities or in situations where moist dressings were preferred. It became very obvious, however, that more rapid success was being obtained with the 5% solution of chloramphenicol in propylene glycol. Since the propylene glycol has no bacteriostatic properties, the effectiveness of the solution is presumably due to the fact that it can permeate more adequately into the deeper recesses. Routine swabs were taken before dressing, which was done daily if possible; but in several cases this could not be done, because of intervening surgery, which interrupted the bacteriological investigations for several days.

Tables I and II show that in the thirty cases treated the wounds were rendered free from infection by the usual pathogens in an average of 3–5 days, some wounds becoming sterile even sooner. The treatment was usually continued for several days after the first negative swab had been obtained. When negative swabs had been obtained on several successive days, treatment was discontinued. This sometimes led to a recolonising of the wound by pathogens, but often the area remained free from bacteriologically detectable infection for several days and invariably continued to improve clinically.

During the treatment of several of these cases, especially those in which there had been delayed wound healing before treatment, there was a dramatic clinical improvement in the wounds, which suddenly started to take on a new power of regeneration. This had also been noted by Lewis and Gray (1951).

BACTERIOLOGY

As already mentioned, most of the organisms encountered were pencillin-insensitive. The commonest was *Staph. aureus*, which was consistently insensitive to penicillin and sulphonamide, and usually to streptomycin as well. This pathogen was present either in pure culture or in association with other resistant organisms, such as *Ps. pyocyanea*, *Proteus vulgaris*, and coliforms.

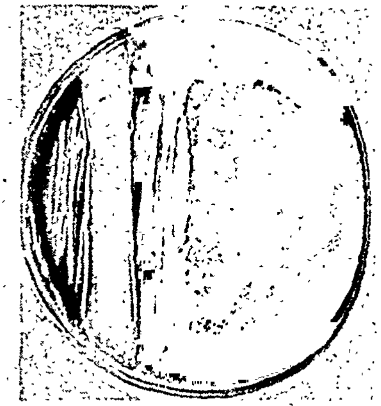
Fig. 2—Zone of inhibition produced by 2·5% chloramphenicol on overnight culture of *Proteus vulgaris*.

The swabs were inoculated on a half or a third of a plate of blood-agar and examined after overnight culture, kept for a further twenty-four hours, and re-examined. Colonies were taken off the plates for sensitivity tests, which were undertaken every day on all the bacteria examined. The sensitivity to chloramphenicol, aureomycin, and penicillin was tested by the gutter method (figs. 1 and 2), special note being taken of the sensitivity to 2·5% and 5% chloramphenicol. Sensitivity to streptomycin was determined in broth cultures. Throughout the series only one strain of *Ps. pyocyanea* was found to be insensitive to 2·5% chloramphenicol, and this organism was readily sensitive to 5%. We found that every growth of *Staph. aureus* was readily sensitive to 2·5% chloramphenicol, as were the *Strep. hæmolyticus* and *Proteus vulgaris*. No change in sensitivity took place during the trial. No organism was sensitive to propylene glycol alone.

The accompanying illustrations show clearly the effects of chloramphenicol in vitro (figs. 1 and 2) and in vivo (figs. 3 and 4).

DISCUSSION

Treatment was based on two principles: (1) wound infections respond better to topical than to systemic treatment because of the greater local concentration of the therapeutic substance and the fact that local treatment encourages a better wound toilet; and (2) the most effective agent available should be used. This we feel we have done by using a local application of 5% chloramphenicol either in lactose as a dry powder or in propylene glycol as a solution. In wounds which had previously been heavily infected and had resisted systemic chemotherapy and various forms of local treatment we found that the pathogens were completely cleared in a remarkably short time (tables I and II). This was achieved also with chronic leg ulcers and burns, where even the presence of necrotic tissue did not hinder the effective action of chloramphenicol.

The bacterial clearance so produced often lasted for several days after the application had been discontinued and was invariably followed by a distinct clinical improvement in the appearance of the wound, and often by rapid healing. As shown in table II, the most constant causal organisms were *Ps. pyocyanea* and a penicillin-resistant *Staph. aureus*. These have hitherto been notoriously difficult to eradicate from

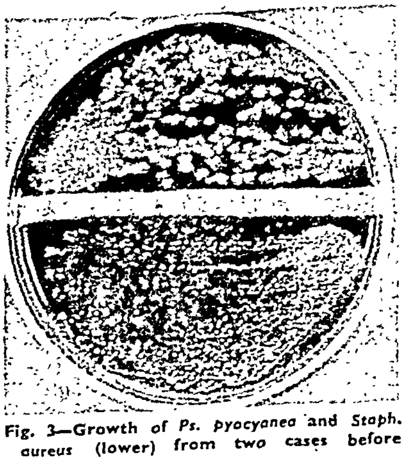
Fig. 3—Growth of *Ps. pyocyanea* and *Staph. aureus* (lower) from two cases before treatment.

wounds, because there was no consistently effective method of dealing with them. However, both these organisms proved equally sensitive to local chloramphenicol (see figs. 3 and 4), being eradicated from wounds within an average time of seventy-two hours, and in some cases in much less time.

An impressive example of the value of this local treatment is shown in the following case :

Case 1.—A girl, aged 18, was admitted for reconstruction of an aplasic right breast, the plan being to carry up a large abdominal flap on a pedicle in staged operations. After preliminary preparation the flap was carried up on its pedicle without incident, but ten days after the operation a fluctuant area developed in the upper inner quadrant of the breast, from which 25 ml. of thick pus was evacuated. Penicillin 250,000 units in 2 ml. was injected into the abscess cavity, which was again aspirated after twenty-four hours. Cultures of the pus revealed penicillin-resistant *Staph. aureus* ; so a full course of systemic aureomycin was immediately begun. Further aspiration was necessary, but the condition appeared to settle within a week. A week later a further operation, to spread the pedicle, was done on the breast. In view of the previous infection the patient was given a second full course of aureomycin postoperatively, but in spite of this she developed within two days a high pyrexia, and complained of severe pain and tenderness in the reconstructed breast. No collection of pus was found at this stage, nor was there any discharge from the wound. The high temperature subsided, but low-grade pyrexia persisted. A week after this second operation the patient developed a profuse purulent discharge from the breast, and culture showed *Staph. aureus* insensitive to penicillin and streptomycin but sensitive to chloramphenicol and aureomycin. The original infection had obviously persisted in spite of the two courses of aureomycin, which is generally considered to be the most effective antibiotic in the treatment of penicillin-resistant staphylococcal infections. Since there was a definite abscess cavity in the breast, it was decided to irrigate it daily with 5% chloramphenicol in propylene glycol. After two days' treatment a swab taken from the abscess cavity was sterile, and the area subsequently remained free from organisms. The discharge rapidly diminished, and the breast healed and remained so.

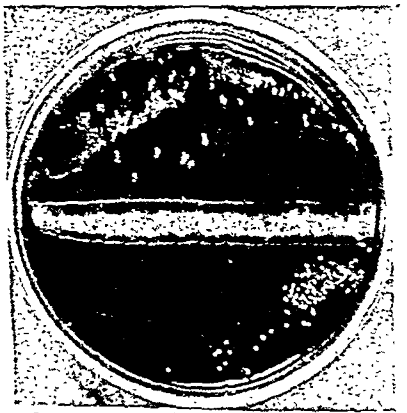

Fig. 4—Growth after two days' treatment with local applications of 5% chloramphenicol.

Case 1 illustrates several important features. It shows once more the extreme efficacy of chloramphenicol in dealing with the penicillin-insensitive organisms, and the superiority of local application over systemic administration. The infection in this case was deep-seated and seemed likely to endanger the newly implanted flap, which of necessity contained much subcutaneous fat. Infection of this, with risk of fat-necrosis, was a serious possibility, but chloramphenicol undoubtedly averted this by rapidly clearing the infection.

Therefore the local application of chloramphenicol in surgery involving repeated operations must be looked on as of great value in reducing time between the operations, and consequently in reducing the period of detention in hospital. This must also be the case in general surgical work, where infection is equally liable to develop, causing delayed wound healing, impaired results, and longer average time in hospital.

Case 2.—A boy, aged 18, had a chronic paronychia, with infection of the nail bed of the great toe, the causal organism being a *Staph. aureus* insensitive to penicillin and streptomycin. A surgical clearance of the affected area was undertaken with a partial excision of the terminal phalanx. Owing to the infection, the operation was covered with systemic chloramphenicol, which was continued for six postoperative days. On the fourth postoperative day there were signs that the suture line was infected, a swab was taken, the area was cleansed, and 5% chloramphenicol in lactose was liberally applied. This was done daily, being combined with foot-baths. Although the wound improved clinically, there was no change in the degree of infection during twenty days' treatment with the powder, there being a constant growth of *Staph. aureus*. In view of this, on the twenty-first day a solution of 5% chloramphenicol in propylene glycol on gauze wicks was applied to the wound. This cleared the bacteria within twenty-four hours, and the wound continued to improve rapidly. The organism isolated was at all times sensitive to 2·5% chloramphenicol.

Case 2 illustrates another of the important findings of this series—that in many cases the solution of 5% chloramphenicol in propylene glycol produced results more quickly than did the same concentration of chloramphenicol in lactose. Tables I and II show that the time taken to clear the wounds with the solution was about half the time taken with the powder, even though the lesions treated with the solution were often less accessible. As stated earlier, we feel that this must be due to a more satisfactory diffusion of the antibiotic in its liquid vehicle, because the propylene glycol has no inherent bactericidal activity.

Although we have seen sensitivity reactions, generally in the form of a maculopapular rash, after administration of chloramphenicol by mouth, we have seen none following local administration. On the other hand, Lewis and Gray (1951) mention two cases in which allergic reactions developed which responded well to anti-histamine drugs, but they are uncertain whether the precipitating cause was the chloramphenicol or some other antigen.

The side-effects of systemic chloramphenicol, caused by deficiency of vitamin-B complex, especially riboflavine, do not follow the local administration of chloramphenicol. This again is obviously an advantage because it avoids the necessity for the simultaneous administration of additional vitamin-B complex.

According to Seltzer et al. (1950a and b) antibiotics seem to have an enhancing effect on candida. We have come across one case in which a person developed a thrush infection of the mouth following systemic chloramphenicol, and Harris (1950) reported the development of infection with candida in patients treated with systemic chloramphenicol, but to date we have had no demonstrable case of candida infection either at the site of treatment or elsewhere.

Local chloramphenicol, combined with surgery where needed, therefore seems to be the most satisfactory agent for clearing established wound sepsis due to penicillin-insensitive organisms, and a useful adjunct to careful technique in the prevention of wound infection.

SUMMARY

Local applications of 5% chloramphenicol (chloromycetin), either as a powder in lactose or as a solution in propylene glycol, were used to obtain a rapid bacterial clearance of a wide variety of wounds infected by penicillin-resistant or insensitive organisms.

The chief organisms encountered were *Ps. pyocyanea*, *Proteus vulgaris*, and penicillin-resistant and streptomycin-resistant *Staph. aureus*. All but one case were sensitive to 2·5% chloramphenicol. No organism became more resistant during or after treatment.

The bacterial clearance in thirty cases was obtained in an average time of 4 or 5 days ; in many cases the time was shorter, especially in cases treated with chloramphenicol in propylene glycol, which seemed more effective than a powder containing the same concentration of chloramphenicol.

No case failed to respond either clinically or bacteriologically to this local therapy, although twenty-eight out of thirty cases had failed to respond appreciably to alternative local treatment and/or systemic chemotherapy. After local chloramphenicol many responded dramatically and all showed improved wound healing.

No local or generalised allergic phenomena or deficiency of vitamin-B complex developed in any of the cases treated.

Local chloramphenicol in penicillin-insensitive wound infection is a most useful adjunct to surgery, and there is a wide scope for its future use.

We wish to thank our colleagues, Mr. Patrick Clarkson, Mr. W. G. Holdsworth, and Mr. C. R. McCash, for allowing us to treat their cases; Mr. Clark of the bacteriological department, Mr. Ferrill and Mr. Ruddel of the photographic department, Mrs. Inwood of the dispensary, and the ward sisters for their help; and Dr. Robert Hodgkinson of the department of clinical investigation, Parke, Davis & Co. Ltd., for his constant help and assistance in this work and for supplies of chloramphenicol.

REFERENCES

Alderson, W. E. (1951) *Lancet*, ii, 224.

Altemeier, W. A., Culbertson, W. R. (1951) *J. Amer. med. Ass.* 145, 449.

Anderson, K. F., Ellis, F. G. (1951) *Brit. med. J.* ii, 1067.

Clark, A. M., Colebrook, L., Gibson, T., Thomson, M. L. (1943) *Lancet*, i, 605.

Copplesou, V. M. (1951) *Ibid*, ii, 65.

Garrod, L. P. (1951) *Brit. med. J.* i, 205.

Gilles, H. M. (1951) *Ibid*, ii, 218.

Harris, H. J. (1950) *J. Amer. med. Ass.* 142, 161.

Jackson, D. M., Lowbury, E. J. L., Topley, E. (1951) *Lancet*, ii, 137.

Kilner, T. P., Peet, E., Calnan, J. S., Kernahan, D. A. (1951) *Brit. J. plastic Surg.* 4, 74.

Leopold, I. H. (1951) *Arch. Ophthal., N.Y.* 45, 44.

Lewis, R. S., Gray, J. D. (1951a) *Brit. med. J.* ii, 939.

— — (1951b) *Lancet*, ii, 208.

Magnuson, W. H. B. (1951) *Ibid*, p. 178.

Magnol, F. (1950) *Arch. Ophthal., Paris*, 10, 636.

Newman, B. A., Feldman, F. F. (1951) *Arch. Derm. Syph.* 64, 212.

Pulaski, E. J. (1951) *J. Amer. med. Ass.* 145, 456.

Seltzer, S., Bender, I. B. (1950a) *Oral Surg.* 3, 1270

— — (1950b) *J. dent. Res.* 29, 825.

Wilson, C. (1948) *Lancet*, ii, 445.

PLASMA-CYSTINE LEVELS IN CYSTINURIA

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NORMAL people excrete in their urine 40–80 mg. of cystine per day (Reed 1942), but in cystinuria with stone formation the daily excretion of cystine is some ten to twenty times this amount. This higher output appears to be regularly associated with a greatly increased urinary excretion of the basic amino-acids lysine and arginine (Dent and Rose 1951).

Cystinuria [illegible] tributed to some failure in the [illegible] of cystine, leading to an accumulation of this amino-acid in the body and its consequent excretion in large quantities in the urine. The exact nature of this postulated block in cystine metabolism has, however, always been somewhat obscure, and the discovery that both lysine and arginine are also excreted in excess has complicated the issue because there is no obvious connection between the intermediary metabolism of these amino-acids and that of cystine.

An alternative hypothesis is put forward by Dent (1949), who suggests that the anomaly in cystinuria is of renal origin. The renal tubules, he thinks, may be unable to reabsorb the cystine, lysine, and arginine normally present in the glomerular filtrate, and these substances therefore appear in large quantities in the urine. Viewed from this standpoint cystinuria could be regarded as analogous to renal glycosuria rather than to, say, phenylketonuria.

COMPARISON OF PLASMA-CYSTINE LEVELS IN CYSTINURICS AND NORMAL PERSONS

Normals				Cystinurics			
Subject no.	Sex	Age (yr.)	Cystine in plasma ultrafiltrate (mg. per 100 ml.)	Subject no.	Sex	Age (yr.)	Cystine in plasma ultrafiltrate (mg. per 100 ml.)
1	M	30	0·65	1	F	17	0·86
2	M	31	1·07	2	M	59	0·86
3	M	27	0·80	3	M	39	0·90
4	F	24	1·32	4	M	39	0·49
5	M	41	0·98	5	M	25	0·38
6	M	30	0·56	6	M	42	0·55
7	M	38	1·12	7	M	31	1·04
8	M	26	0·74	8	F	23	0·57
9	F	22	0·55	9	F	7	0·53
10	F	36	0·94				
11	M	26	0·19				
Mean ..		..	0·82	Mean ..		..	0·60
Standard deviation ..			0·31	Standard deviation ..			0·23

A comparison of the cystine levels in the blood-plasma of cystinuric and normal persons is of some importance in attempting to test these two hypotheses. On the view that cystinuria arises from some kind of block in the intermediary metabolism of cystine one might expect that in this condition cystine would accumulate in the body-fluids, and that consequently the cystine level in the blood-plasma would be considerably higher than that in normal people. On the view that cystinuria is a renal peculiarity no such rise of plasma-cystine would be expected; if anything the level might be slightly lower than normal.

The plasma-cystine levels in a few cystinurics and normal people have been estimated chromatographically (Dent and Rose 1951) and microbiologically (Dent et al. 1951). No appreciable difference between the normals and the cystinurics was found. However, in view of the difficulties involved in both these techniques of quantita[illegible] o-acids, it seemed desirable to [illegible], using a third and quite different method of estimation—namely polarography (Brdicka 1933).

Ultrafiltrates of blood-plasmas from 11 normal adults and 9 cystinurics were examined. All the cystinurics except 1 were known to have formed cystine stones; and this patient regularly produced cystine crystals in his urine. In addition the diagnosis of cystinuria, as redefined by Dent and Rose (1951), was confirmed by clinical examination and by filter-paper chromatography, and the high cystine output by polarography of the urine.

1 ml. of a 1 : 1 dilution of heparinised plasma ultrafiltrate with water was used in each estimation. This was added to 3·9 ml. of a *N* ammonia and *N* ammonium-chloride buffer containing 0·1 ml. of M/10 cobaltous chloride. The current voltage curve was recorded between −0·8 V and −1·8 V. The relation between the current developed at the maximum of the catalytic wave and the cystine concentration was determined with standard solutions of cystine.

The results are presented in the accompanying table. The mean of the plasma-cystine levels in the cystinurics is slightly lower than the mean of those in the normal persons. This difference is not statistically significant. These findings tend to support the view that cystinuria arises from some peculiarity in renal function rather than from some disturbance in the intermediary metabolism of cystine.

We wish to thank Mrs. R. Jacobs for technical assistance, nd Dr. C. E. Dent for permission to study his patients.

REFERENCES

rdicka, R. (1933) *Collection czechoslav. Commun.* 5, 238.
ent, C. E. (1949) Biochemical Society Symposia: no. 3.
— Heathcote, J. G., Joron, G. E. (1951) Personal communication.
— Rose, G. A. (1951) *Quart. J. Med.* 20, 205.
eed, G. (1942) *J. biol. Chem.* 142, 61.

Preliminary Communication

CORTISONE-INDUCED "PRECOCIOUS PUBERTY" IN RATS

In the course of experiments designed to study how he growth of weanling male Wistar rats is affected by the ong-continued administration of cortisone and by the ddition of various substances (such as fat, fat-extracted iver, or desiccated thyroid) to the diet, it was noticed that priapism developed in some rats. The penis became prominent, engorged with blood, and cyanotic, and the prepuce, at first at least, was swollen and discoloured (see figure). This priapism was noticed as early as the 16th day or as late as the 27th day after the start of treatment with cortisone and persisted, with 2 exceptions, till necropsy on the 28th day. Preliminary analysis of our data shows that the only factor common to the rats showing this phenomenon was the administered cortisone (table I).

TABLE I—RELATION OF PRIAPISM TO CORTISONE

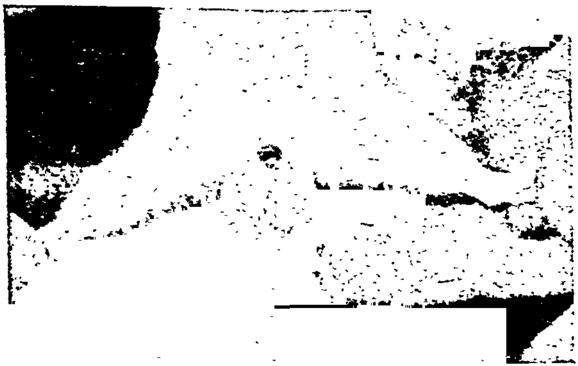
Treatment	No. of rats	No. with priapism
* Cortisone with or without 0·05% thyroid in the diet	28	14
* Cortisone with 0·1 or 0·2% thyroid in the diet	11	3
No cortisone, with or without 0·05% thyroid in the diet	28	0

* 'Cortone' Merck 1·5 mg. subcutaneously daily for 6 days a week. (Supplied by Dr. Elmer Alpert, of Merck & Co.)

TABLE II—TESTICLE/BODY-WEIGHT RATIO IN RELATION TO CORTISONE

No cortisone		Cortisone	
Testicle (mg.)/ body-weight (g.)	No. of rats	Testicle (mg.)/ body-weight (g.)	No. of rats
11·7	4	18·0	4
12·2	3	19·9	4
13·2	4	16·4	4
13·6	3	17·4	4
11·5	3	16·6	4
12·4	4	—	—

Table II shows that the testicle/body-weight ratio was also altered in these rats. According to Donaldson[1] rats of the same body-weight as those used in the present experiment have a testicle/body-weight ratio between 10 and 13.


Enlargement of genitalia.

All these rats were prepubertal at the start of the experiment. Though litter-mate controls were lacking, the altered testicle/body-weight ratios are sufficiently uniform to be significant. The question arises whether the picture produced here has any resemblance to macrogenitosomia præcox in children. Experiments are now being planned to see if the changes described are due to a direct effect of cortisone, and to define the part played by other endocrine organs.

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The Medical School,
University of Birmingham.

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[1] H. H. Donaldson. The Rat. Philadelphia, 1924.

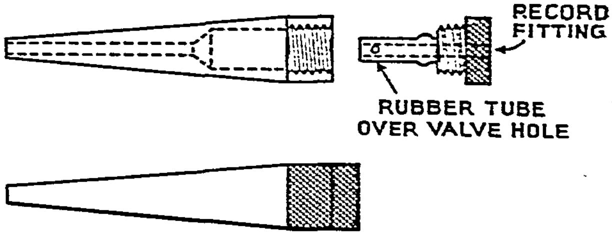
New Inventions

NON-RETURN NOZZLE FOR USE WITH A FOLEY-TYPE URETHRAL CATHETER

The nozzle illustrated has been designed for use with the Foley type of indwelling urethral catheter. The bag of this type of catheter cannot be filled satisfactorily with a 'Record' syringe owing to its trumpet-shaped end. Some form of nozzle is therefore essential.

To prevent the fluid from escaping after filling the bag, screw-clips are often applied to the catheter, or a silk ligature is tied round it. Both of these measures are wasteful because the catheter is soon ruined and becomes unserviceable. A wooden spigot does not make a sufficiently watertight junction and will leak.

The nozzle tapers and has circular ridges on it so that it will make a firm fit with any size of Foley catheter.



A simple type of non-return valve is incorporated, so that the bag of the catheter can be filled accurately with the required amount of fluid, and the nozzle left in situ. The nozzle can easily be dismantled with a coin—as in refilling a petrol lighter—for inspection of the valve tubing, which perishes in time.

The nozzle may seem unnecessarily large and heavy, but its size makes it less likely to get lost in the ward or in the steriliser. It should be strapped securely to the patient's thigh, and this will prevent too great a drag on the catheter.

The nozzle has proved satisfactory in constant use at St. Paul's Hospital for four months. It was made for me by the Endoscopic Instrument Co., of 62, Shirland Road, London, W.9.

K. Whittle Martin, F.R.C.S.
Registrar, St. Thomas's Hospital London.

"... The human make up is certainly changing; we alter ourselves merely by knowing more about ourselves yearly. Perhaps, under the thrust of scientific inventions, the change will proceed still quicker. Perhaps, after the storms have swept by and the aeroplanes crashed into one another and wireless jammed wireless, a new creature may appear on this globe, a creature who, we pretend, is here already: the individual."—E. M. Forster. *Two Cheers for Democracy.* London. 1951; p. 22.

Reviews of Books

Recent Advances in Clinical Pathology

2nd ed. Editor: S. C. DYKE, D.M., F.R.C.P. London: J. & A. Churchill. 1951. Pp. 575. 40s.

THE second edition of this valuable work appears after only four years. Yet so great have been the advances in laboratory medicine that the book has had to be entirely recast. Occasional chapters have been rewritten but most are new, so that it would be more correct and perhaps fairer to call this volume the second of a series rather than a second edition. The editors, in fact, point out that it is meant to supplement the first edition and "what at first sight seems to be a rather curt dismissal of the work of the previous authors is actually a tribute to its quality, because the contributions made by them in 1947 are still, for practical purposes, valid to-day." The 30 contributors are acknowledged authorities; their essays are full of up-to-date information; and we can be sure of seeing this edition, like its predessor, on the "practical" bookshelf of pathological laboratories throughout the world.

Treasury of Human Inheritance

Editor: L. S. PENROSE, M.D. Vol. 5. *On Hereditary Digital Anomalies.* Part I. *On Brachydactyly and Symphalangism.* JULIA BELL, M.A., F.R.C.P. London: Cambridge University Press. 1951. Pp. 31. 12s. 6d.

MINOR malformations of the hands and feet early attracted the notice of geneticists. They are easily studied by naked-eye and X-ray examination. They have little effect on fitness, so that where dominant genes are responsible some impressive pedigrees have been collected with affected members in six or more generations. Dr. Julia Bell's account of these malformations follows the traditional pattern of the *Treasury.* She gives a detailed account of all the published families, together with an analysis of the variations that occur in the form of the malformations within the same family and between different families. The anomalies fall into about seven main groups, and within the same family the affected members usually all belong to the same group. All the pedigrees suggest dominant inheritance; in some of the groups it is probable that all those carrying the gene are affected, but in others occasional skips occur.

A genetic study based on recorded families has its limitations. It tells us nothing about the frequency of the condition nor the proportion of instances in which the anomaly occurs in only one member of a family with no suggestion of genetic determination. But within these limitations the monograph could hardly be bettered.

Adrenal Cortex

Transactions of the Second Conference, Nov. 16, 1950, New York. Editor: ELAINE P. RALLI. New York: Josiah Macy Jr. Foundation. 1951. Pp. 209. $3.

Proceedings of the Second Clinical A.C.T.H. Conference

Editor: J. R. MOTE, M.D. London: J. & A. Churchill. 1951. Vol I; pp. 531. Vol II; pp. 716. 60s. each.

BOTH these books are verbatim reports of what has been said by experts in conference. It is a pity that, as reports from the front line of medical research, they have taken so long in transit.

The smaller book deals mainly with the theoretical background of adrenal chemistry and physiology. There are five main topics: the chemistry of A.C.T.H. (led by H. Li); the regulation of pituitary adrenocorticotropic activity (led by G. Sayers); the relation of the adrenal cortical hormones to the hypersensitive state (led by T. F. Dougherty); hyaluronidase and the adrenal cortical hormones (led by J. Opsahl); and further clinical studies with A.C.T.H. and adrenal cortical hormones (led by G. W. Thorn). The text is presented rather like the script of a play, making it easy to picture the speakers at the conference. Hobby-horses are ridden across these pages, and are stalked by the other experts. The reader can conjure up a vivid impression of the scene when Li has, by means of a patient, learned, and logical exposition, built up a theory of the chemistry of "small molecular" A.C.T.H., only to have it rudely upset by Astwood's pronouncement that the starting material Li had used was probably at least 99% impure. Opsahl's review of the rather confusing relation between hyaluronidase and the adrenal cortex, and Sayer's exposition of the physiological mechanisms governing corticotropin release and allied questions are to be particularly commended. However, the book is by no means confined to the topics listed, for the discussions roamed over many related subjects. Many small errors are probably due to hasty editing and proof-reading.

The two large volumes which contain the proceedings of the Second Clinical A.C.T.H. Conference testify to the enormous amount of research that has gone on since therapeutic adrenal stimulation for diseases other than those of the pituitary became possible on a large scale. A year ago, at the first conference, it seemed that most aspects of A.C.T.H. therapy had been touched on. Now we see specialties appearing within specialties, and in addition interesting newcomers take the stage—such as "Black Widow spider bite," "North American blastomycosis," and "Hunner ulcer." The two volumes are subtitled, rather hopefully, "Research" and "Therapeutics." But allocation of subjects is often unpredictable. He who seeks information on the effect of A.C.T.H. on liver disease, for example, must not be dismayed if he cannot find this under "Infectious Disease and Liver Disease"; he has only to turn to "Adrenal Gland and Hemopoietic System" to find three papers on his subject. But this is a minor failing in a book of great value to all those who seek to keep up with the great tide of research that the mass-production of adrenal cortical hormones has liberated.

Much of the research into the therapeutic uses of A.C.T.H. has outstripped knowledge of its pharmacology, and particularly of the factors which influence the response of the patient; for it is clear that, on the one hand, batches of A.C.T.H., identical on animal assay, may provoke different degrees of response in man; while, on the other hand, the same patient's response to repeated doses of the same batch of hormone will itself vary from week to week. These limitations make some of the quantitative studies of qualitative value only.

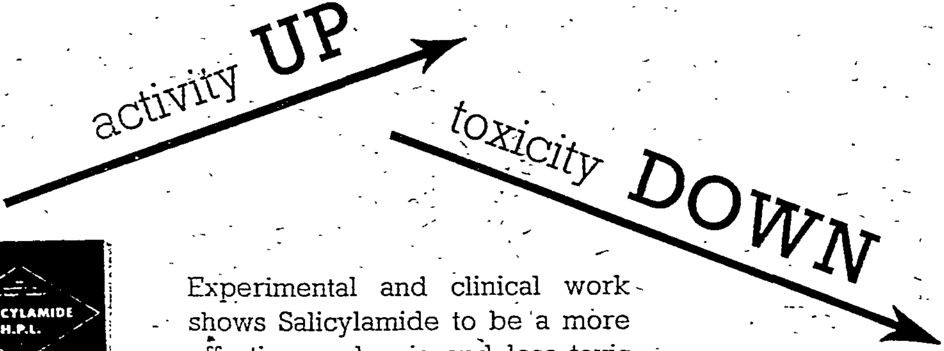
Fractures and Joint Injuries

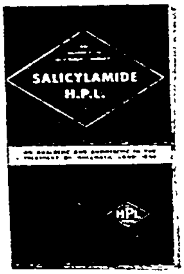
Vol. I. 4th ed. Sir REGINALD WATSON-JONES, M.CH. ORTH. LPOOL, F.R.C.S. Edinburgh: E. & S. Livingstone. 1952. Pp. 443. £6 (with Vol II, when published).

EVIDENTLY it is possible to gild the lily. In this new edition, appearing nine years after the last, the text has been extensively rewritten and many fresh illustrations have been added. New material, dealing with wound shock, the adaptation syndrome, chemotherapy, bone-grafting, and medullary nailing, almost doubles the space allotted in the first edition to the general principles of fracture treatment. The section on pathological fractures gives an exhaustive review of local and systemic disease of the skeleton. If the slightly polemical flavour of this edition and its increasing emphasis on a personal view makes it rather less valuable as a guide for the newly qualified, it is more valuable than ever to the young orthopædic surgeon who is forming his own opinions. Thus the chapter on the reaction of bone to metal is a vigorous attack on the accepted view that contact-compression is an important and desirable factor in promoting union. The sections on open fractures, joint wounds, and bone-grafting are magnificent and magnificently illustrated with colour photographs, though it is a pity that Phemister's method of simple onlay grafting without disturbance of the fracture site for non-union of the tibia is not specifically mentioned. Volume II, on the management of individual fractures, is to appear later in the year.

Anemias (Madrid: Manuales Ibys. 1950. Pp. 393.).—This is interesting as an example of a Spanish textbook. It describes the anæmias very thoroughly. Sometimes the syndromes are split into more subdivisions than are customary in this country, but the teaching is sound and conforms with Anglo-American views. The notably representative bibliography shows that Dr. Valentine de la Loma is well acquainted with modern English, American, and European work. The 12 colour plates, however, are poor.

SALICYLATE THERAPY





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Lancet.	1951,II,629
Dtsch. med. Wschr.	1951,76,1312

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THE LANCET

LONDON: SATURDAY, MARCH 15, 1952

The New Treatment for Tuberculosis

The information already given[1] about the clinical use of isonicotinic acid hydrazide ('Nydrazid' Squibb, 'Rimifon' Roche) in tuberculosis can now be supplemented; and we publish on p. 557 an account of the first paper on this subject read before a medical society.

Though nicotinic acid hydrazide was synthesised in 1912,[2] its therapeutic value was not appreciated, and its present application to tuberculosis arises primarily from the treatment of that disease with thiosemicarbazone, which we owe to Domagk,[3] the discoverer of 'Prontosil.' Last year Fox[4] gave an account of isonicotinaldehyde thiosemicarbazone and related compounds, and many of these are being further investigated. Meanwhile the clinical trials are being made chiefly with isonicotinic acid hydrazide, which Grunberg and Schnitzer[5] found to have a profound effect on tuberculosis in mice, and to a less extent with its isopropyl derivative ('Marsilid' Roche). The reports both of the experimental work and of the treatment of patients at the Sea View Hospital, New York,[6] suggest that these drugs are much more potent that any previously employed. It is, of course, a pity that announcements were made in the public press in a way which may have raised unwarranted hopes and given some wrong impressions. In fact we have reason to believe that none regret this premature publicity more than those who have been responsible for the synthesis of the new drugs, and those who have taken an active part in testing their value in practice. On the other hand, considering the extraordinary clinical effects now described, it is remarkable that the news did not leak out until nearly six months from the inception of the clinical trials. Already a number of communications are in the press, and a preliminary symposium has been published by the Sea View Hospital[7] which provides information on a professional basis.

Though it is understood that about 190 patients have now been treated, Selikoff et al.[6] confine their report to the first 92. These had been observed for an average of nine months in the same wards before the institution of the new therapy, and in all cases tuberculosis was progressing in spite of treatment. Though the condition of none was "terminal" these patients represented as unpromising a type of clinical material as could reasonably be selected: 17 had extrapulmonary tuberculosis, including genito-urinary, perirectal, aural, laryngeal, and other complications such as empyema and bronchopleural fistula, and 1 had a severe tuberculous glossitis. During the administration of the new drugs no other medication was practised, except that unilateral pneumothoraces were continued where the disease in the contralateral lung was uncontrolled. The dosage ranged from 2 to 4 mg. of isonicotinic acid hydrazide, and from 2 to 10 mg. of its isopropyl derivative, per kg. body-weight, and the drugs were usually given by mouth three times a day in equal doses after food. All 92 patients exhibited response to treatment, and up to the time of publication there were no deaths. Reduction of temperature was an almost immediate result, occurring as a rule in the first week, or less often in the second. Cases which showed a subsequent rise in temperature were found to have intercurrent non-specific respiratory infection. Weight increases verged on the dramatic for patients suffering from this type of tuberculous disease: they ranged from 3–5 lb. to 7–10 lb. a week. The increase in weight was always associated with disappearance of most of the toxic symptoms, and with an increase in appetite, which sometimes reached "insatiable" proportions: "three bowls of cereal and five eggs for breakfast have become a commonplace." (The possibility of this weight gain being due to water-retention has been eliminated.) Relief from cough and expectoration was also rapid. Within five weeks, 25% of the patients had a negative sputum on concentrated smear examination and after gastric lavage; a further 28% showed an occasional positive sputum, but usually the sputum was negative on concentrated smear; and though the remainder of the patients continued to show a positive sputum on unconcentrated smear the bacillary counts were all "in the lower Gaffky range."

Radiologically, simultaneous diminution in the size of three or more cavities within the same lung was noted in 3 cases, and spontaneous closure of an isolated cavity was repeatedly observed. Of great interest is the fact that negative sputum and gastric lavage were observed in patients whose cavities remained patent: of 23 patients with negative sputa, cavities were still patent on X-ray examination in 14, and probably patent in a further 7. In the cases with extrapulmonary tuberculosis, the results equalled the best obtained with streptomycin. Another striking feature of the trial is that, at the time of report, the drug had apparently had comparatively little toxic effect, especially where the lower doses were used. Vertigo was noted, especially in the older patients, but it was usually slight and may be of vasomotor origin. Constipation can be severe, but is easily overcome by routine treatment, and no serious urinary, visual, or other complications are described, though euphoria, exaggerated tendon reflexes, and a transitory Babinski's sign have been seen in patients receiving the higher doses. Evanescent proteinuria and eosinophilia of severe degree have also come to light, but it is too early to judge the significance of these manifestations, which nearly all occurred with the higher doses. No resistant forms of bacilli have so far been observed.

From all this it will be evident that the isonicotinic acid hydrazides have had an excellent debut; but the weight of critical opinion is still to come and will no doubt soon reach avalanche proportions. The combination of negative sputum, relatively large ring shadows in the X-ray film, and absence of apparent toxæmia is in itself a new conception to those who are familiar with the pathology of advanced chronic bilateral caseous-pneumonic pulmonary tuberculosis.

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[1] See *Lancet*, March 1, 1952, p. 454.
[2] Mayer, H., Nally, J. *Mschr. Chem.* 1912, 33.
[3] Domagk, G., Behnisck, R., Mietzch, F., Schmidt, H. *Naturwissenshaften*, 1946, 10, 315
[4] Fox, H. H. 12th Int. Congr. Pure and Applied Chem. Sept. 9–13, 1951; *Chem. Engg News*, Sept. 24, 1951, p. 3964.
[5] Grunberg, E., Schnitzer, R. J. *Quart. Bull. Sea View Hosp.* 1952, 13, 3.
[6] Selikoff, K. J., Robitzek, E. H., Ornstein, G. G. *Ibid*, p. 17.
[7] *Quart. Bull. Sea View Hosp.* 1952, 13, no. 1.

Even if we have no more than a drug or series of drugs which will reduce the number of tubercle bacilli, without annihilating all those present, the expectation of life for many tuberculous patients should be increased; and the effect of such a reduction in the volume of infection in the community—provided it could be maintained—needs no emphasis. It cannot be made too clear, however, that even if all the hopes are fulfilled we shall not be able to take advantage of the new remedies unless we continue to extend and perfect our methods of case-finding and make our methods of bacteriological diagnosis more precise.

Artificial Respiration

In this country the Schafer method of artificial respiration has for many years been the most popular, and undoubtedly it has saved many lives. Recent American work seems to suggest, however, that other methods may be better.

Emergency artificial respiration poses two problems: (1) what is best for the patient? and (2) what is practicable for the operator? With these questions in mind the American workers[1-3] have compared the following methods:

1. The Schafer prone-pressure.
2. The Silvester arm-lift/chest pressure.
3. The Nielsen, in which the patient is prone and the thorax is alternately compressed below the scapulæ and then just raised off the ground by the patient's upper arms.
4. The hip-lift combined with back-pressure (H.L.B.P.).
5. The hip-roll/back-pressure (H.R.B.P.), which is a variant of no. 4.

All these methods except the Schafer, in which only expiration is forced, involve active compression and active expansion of the chest—that is, they are push-pull methods. The investigations included records of tidal volume, pulse-rate, systemic blood-pressure, pulmonary-artery and right-auricle pressure, arterial oxygen saturation, and electrocardiographic changes.[1] Blood-pressure was recorded and blood samples taken by means of arterial catheters. The tests were made as nearly as possible under emergency conditions of anoxia, mostly on healthy young adults rendered insensible by anæsthesia and immobile by tubocurarine; but some of the subjects were conscious. Other tests were made during recovery from anæsthesia, and a few on corpses that were not yet rigid.

The figures obtained by the various groups of workers differed somewhat; but their conclusions were identical. All agreed that the Schafer method gave the smallest tidal volume (485–296 c.cm.), while the H.L.B.P., Silvester, and Nielsen gave 1140–680 c.cm., 1087–795 cc.m., and 1060–474 c.cm. (The values given by SCHAFER were 520 c.cm. for his method, and only 115 c.cm. for the Silvester). The lowest volumes were recorded in women and in patients with intracranial lesions. Back pressure gave significantly greater ventilation than either prone or scapular pressure. Spirometer tracings showed that with the Schafer method all the ventilation was accomplished in the inspiratory reserve volume—i.e., the supplemental air.[3] Of this SCHAFER himself was well aware; and it was part of this reserve of about 1500 c.cm. that he set out to use.[4] It is difficult to see why the two sets of figures differ as greatly as they do. SCHAFER tested conscious subjects; but so did one group of Americans, whose value for the Schafer method (466 c.cm.) is fairly close to his, while their figure for the Silvester method is 1087 c.cm. The conscious subject may unwittingly help or hinder the manipulator, and presumably it is in this uncontrollable factor that the difference originates.

Since the normal tidal volume is 450–500 c.cm. Schafer's method might seem to provide adequate ventilation, and the high ventilation obtainable by other methods might be judged unnecessary. On the other hand, the patient requiring resuscitation has been deprived of air; hence his arterial oxygen is low and his carbon dioxide high; and he is in need of hyperventilation, at least for a short time. Moreover, as the American studies show, methods that produce hyperventilation in the healthy are only just sufficient with apnœa due to a pathological condition. It was found that in the nearly dead the elasticity of the tissues was so low that after release from two or three forced expirations intrathoracic pressure was only just below atmospheric pressure, and passive inspiration sometimes filled hardly any more than the dead-space volume.[2] There is evidence, too, that the heart often fails before respiration, and that this failure is due not so much to peripheral vasodilatation and low blood-pressure as to poor oxygen supply to the heart itself. When a resuscitating pump was used, the heart recovered with as little as 3% oxygen in nitrogen, provided that the blood-pressure had not fallen below a critical level.[2] Commonly in emergencies only manual methods are practicable; and unless the lungs are thoroughly expanded a large part of the blood passes through closed alveoli where no gas exchange can occur, and thus extremely "venous" blood enters the left heart. Although the heart can recover with little oxygen, the margin of time between possible recovery and inevitable death proved short—about 20 seconds.[2] At 12 respirations per minute, that is only 4 respirations. This shows the need for introducing as much oxygen as quickly as possible into the coronary circulation. Furthermore, if apnœa has lasted a little time, circulation and respiration may recover, yet the central nervous system may be irretrievably damaged. Rarely the patient survives in a decerebrate condition; more often the nervous damage leads to death a few days after so-called recovery.

The second problem—namely, which method is most practicable—again has two aspects. Can the most efficient method be taught to, and carried out by, those who will have to do it; and can it be continued for a long enough time? A number of trials with Service men and women showed that all the methods can be taught quickly and be well performed. The two that were most accurately performed were the Silvester and the Nielsen. Both men and women could perform all the methods for 15 minutes; the H.L.B.P. was the most tiring, and the H.R.B.P. the least efficiently carried out. Thus, from the point of view both of good ventilation and of good manipulation, the choice lay between the Silvester and the Nielsen.[1] Surprisingly, the American workers suggest that 15 minutes' manipulation is enough except where apnœa is due to carbon monoxide or drugs.[2] Resuscitation after drowning raises other considerations. Almost inevitably water has been inhaled, with consequent changes in blood concentration. After submergence in fresh water for 3 minutes 72% of the blood may consist of "drowning water." With sea water, on the other hand, osmotic forces draw 30–40% of the water of the blood into the lungs in 1–2 minutes, while salts enter the blood in high concentration. Thus in the one instance there is hæmodilution, and in the other hæmoconcentration. Hæmodilution is the more serious condition, and may give rise to ventricular fibrillation in a short time.[5] Thus, after drowning recovery of respiration may not be enough: the composition of the blood may have to be corrected.

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[1] *J. appl. Physiol.* 1951, 4, no. 6.
[2] Swann, H. G. U.S.A.F. Air Materiel Command: technical report no. 6006. October, 1950.
[3] Gordon, A. S., Sadove, M. S., Raymon, F., Ivy, A. C. *J. Amer. med. Ass.* 1951, 147, 1445.
[4] Schafer, E. A. S. *Ibid.* 1908, 51, 801.

The conclusions of the American workers may be summarised as follows. Compared with other methods, the Schafer gives only a small tidal volume. In pathological condition and in electrocution, the resilience of the lungs and thorax rapidly decreases, and passive inspiration therefore becomes less and less effective. With the Schafer method the lungs are poorly expanded, and thus much of the blood reaches the heart unoxygenated. It is important that oxygen should quickly reach the cardiac muscle and the central nervous system before irreversible changes take place. Therefore, a "push-pull" method is better than one of "push" only. The Nielsen is the method of choice: in it the subject is prone, so that his airway is unlikely to be blocked by tongue, epiglottis, or mucus; and this method can be easily taught and properly executed without undue fatigue for a fairly long time.

With this evidence before us, and twenty years of satisfactory experience of the Nielsen method in Scandinavia, we should perhaps seriously ask whether the Schafer prone-pressure method should still be officially recommended.

The Cause of Simple Goitre

SIMPLE goitre is an ancient affliction of man. Recognisable accounts are to be found in the early writings of most civilised races; and description is usually accompanied by speculation about the cause of the deformity. In 1867 ST. LAGER[6] enumerated 43 hypotheses concerning the causation of goitre, and since his time there have been further additions. SPENCE[7] has lately reviewed the more respectable of these ideas. Perhaps the most striking impression from his review is the extraordinary diversity of the opinions which still hold the field. Even after discarding the older meteorological hypotheses (such as miasmas and temperature variations) there remain a large number of possible nutritional causes (deficiency or excess of minerals, vegetables, or meat), while bacterial agents—which have been ably advocated by Sir ROBERT MCCARRISON—are not yet finally excluded. Nor is it likely that the final analysis will concern only environmental factors: the constitution of the individual, interaction with other endocrine glands, and possibly genetic factors may also be important. Whatever else it may be, the cause of simple goitre is not simple.

Though probably still a long way from the centre of the mystery, modern research has contributed at least one important simplification. This is the doctrine that, whatever the ultimate cause, a goitre is always a compensatory phenomenon. Something hinders the thyroid in its task of producing thyroxine, and as thyroxine declines in the blood the anterior lobe of the pituitary is stimulated to make more of its thyrotropic hormone; this reacts on the thyroid, causing hypertrophy and multiplication of its secreting units, the acini; the thyroid enlarges, and also works more efficiently. The obstacle to the manufacture of thyroxine is overcome, and the price is a goitre. On this analysis, the cause of goitre is anything which prevents or hinders the formation of thyroxine. Since each molecule of this substance contains four atoms of iodine, it is easy to see that lack of this relatively rare element cannot fail to cause goitre. The remainder of the thyroxine molecule comes from tyrosine; so dietary deficiency of this amino-acid (and of phenylalanine, from which it is readily formed) could conceivably also give rise to goitre: indeed, goitre has been produced in rats fed on a diet whose protein is poor in these amino-acids.[8] This deficiency is unlikely, however, to be found in Western diets.

Even when the necessary materials are present, however, formation of thyroxine can still be prevented. The thiocyanate ion can prevent the thyroid from concentrating iodide from the blood. For land animals, whose intake of iodine is normally scanty and erratic, this concentration of the iodide ion is an essential first step in the manufacture of thyroxine, though it becomes redundant if iodine is plentiful in the diet. When thiocyanate was used in the treatment of hypertension goitre not uncommonly resulted.[9 10] Once present it could be made to disappear by stopping administration of the thiocyanate, or by supplementing the thiocyanate with thyroid extract (which relieved the thyroid of the necessity of making thyroxine) or with iodide (which relieved the thyroid of the necessity of concentrating this ion). Thiocyanate goitre thus behaved exactly as was to be expected theoretically; and this greatly strengthened the general hypothesis that goitre is a compensatory phenomenon. The only mysterious feature was that it arose in only some of the patients treated with thiocyanate in an identical way. Varying iodine intake may partially explain this anomaly, but probably an unknown constitutional factor was also concerned. Thiourea and its numerous derivatives do not prevent the thyroid from concentrating iodide; but they do inhibit oxidation of iodide to iodine, and hence make the formation of thyroxine difficult or impossible. The ability of these compounds to cause goitre in the rat is now well known, while their property of preventing thyroxine formation is widely utilised in the treatment of hyperthyroidism. Resorcinol, though chemically unrelated, probably acts in a similar way; and when applied for long periods to chronic ulcers it can also cause goitre and myxœdema.[11] In the rat sulphonamides, too, acting probably by a somewhat different mechanism, can block thyroxine formation and hence cause goitre; but they do not affect the human thyroid.[12]

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[5] Moritz, A. R. *Physiol. Rev.* 1944, 24, 70.

[6] St. Lager, J. Études sur les causes du cretinisme et du goitre endemique. Paris, 1867.

[7] Spence, A. W. Presidential address to section of endocrinology, Royal Society of Medicine, Jan. 23, 1952.

[8] Pal, R. K., Bose, N. M. *Ann. Biochem. exp. Med.* 1943, 3, 99.

[9] Barker, M. H., Lindberg, H. A., Wald, M. H. *J. Amer. med. Ass.* 1941, 117, 1591.

[10] Rawson, R. W., Hertz, S., Means, J. H. *Ann. intern. Med.* 1943, 19, 829.

[11] Bull, G. M., Fraser, R. *Lancet*, 1950, i, 851.

[12] Stanley, M. M., Astwood, E. B. *Endocrinology*, 1947, 41, 66.

The position of the remaining members of Spence's list of possible goitrogenic agents is less well established. Excess of calcium or fluorine, or excess of protein in the diet, have often been said to cause goitre in laboratory animals, but the evidence is contradictory. Further agents no doubt remain undiscovered; but discussion of the possible causes of goitre can most profitably be based on the well-recognised factors alone. Of these factors, the only one which is certainly important in man is iodine deficiency. Where goitre is endemic the iodine content of soil, water, and locally grown vegetables is almost certain to be low. But the converse is by no means clearly true; for goitre is far from rare in places (like London or Boston, Mass.) where iodine supplies are plentiful. The only certain facts about simple goitre are that it can be caused by iodine deficiency, and that iodine deficiency is not the only cause.

The idea that thiourea derivatives might play a part in the causation of human goitre remained somewhat nebulous until Astwood and his colleagues[13] isolated one of these compounds—5-vinyl-2-thiooxazolidone—from turnips and swedes. They showed that this substance had considerable antithyroid activity both in man and in the rat, and that it was present in turnip and swede roots in significant amounts (0·2 g. per kg.). This so far is the only unequivocal demonstration of a powerful goitrogenic substance in a commonly eaten foodstuff. Further work,[14] however, showed that the substance was present in the vegetable roots in a bound and inactive form. The active substance was released on steeping the cut-up roots in water at room-temperature; but the amount of heating commonly used in cooking destroyed the enzyme which releases the active substance. Thus cooked turnips have little or no antithyroid effect; but it is worth remembering that during the winter months raw turnips and swedes are commonly fed to cattle, and thiourea derivatives appear freely in the milk. It therefore remains possible that 5-vinyl thiooxazolidone reaches the human being by this indirect route, which has not so far been investigated. This antithyroid substance is also present in many cruciferous seeds, such as those of cabbage and rape, as well as the seeds and roots of turnip and swede; but it has not been detected in the leaves or flowers of other edible crucifers, such as cabbage or cauliflower. It probably does not account, therefore, for the goitre in rabbits fed on cabbage diets.[15] Since cabbage goitre is readily prevented by adding iodide to the diet it can more reasonably be attributed to thiocyanate, which might be present as such in the cabbage or might be formed in the body as the result of detoxification of organic cyanides. Thiocyanate (or a substance giving the same colour reaction with ferric nitrate) is commonly present in human blood. There is therefore rather more reason to suspect thiocyanates than thiourea derivatives as a factor in the causation of human goitre. There is still no direct evidence that enough of either class of substance is present in our normal diet to favour the appearance of goitre, though enough may be eaten by people with a preference for unorthodox diets and by communities living under conditions of famine. Investigation of the ætiology of a disease as chronic as simple goitre is peculiarly difficult. Usually by the time we see such patients active growth of the gland has long ceased. What we need to know is the composition of the diet the patient ate twenty years previously.

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[13] Astwood, E. B., Greer, M. A., Ettlinger, M. G. *Science*, 1949, 109, 631.

[14] Astwood, E. B. *Ann. intern. Med.* 1949, 30, 1087.

[15] Chesney, A. M., Clawson, T. A., Webster, B. *Bull. Johns Hopk. Hosp.* 1928, 43, 278.

Chloramphenicol *in Penicillin-resistant Infection*

Once again attention is being drawn to the valu of chloramphenicol as a chemotherapeutic agen Early work[1–3] showed that this antibiotic was activ in vitro against gram-negative bacilli, and to a less extent gram-positive and acid-fast bacteria, bu inactive against yeasts, fungi, and protozoa. In mic it afforded no protection against pneumococcal an streptococcal infections, but moderate protectio against klebsiella and shigella infections. This ant biotic, however, gave remarkable protection agains *Rickettsia prowazeki,* the causal agent of louse-born typhus, in chick embryos; and Smadel and Jackson recorded positive results in experimental infectio with viruses of the psittacosis-lymphogranulom group. It was further shown that chloramphenic was absorbed from the intestinal tract of dogs, an that for laboratory animals its toxicity was of th same order as that of streptomycin. The antibiotic therefore, was welcomed as an important agent fo the treatment of rickettsial and possibly virus infec tions; and reports of success in the treatment o louse-borne[4] and scrub[5] typhus and Rocky Mountai fever[6] quickly followed. Psittacosis,[7] lymphogranu loma venereum,[7] and atypical pneumonia[8] were als found to respond. The importance of chloramphenicol however, did not end here. In 1948, during a stud of its effect in scrub typhus,[5] the accidental inclusio of a case of typhoid fever led to the discovery of it effectiveness in this infection also.[9] Then in 1949 milestone in the history of antibiotics was laid whe 'Chloromycetin' (as it had hitherto been called) wa synthesised in the Parke Davis Research Laboratory and given the name chloramphenicol.

Recent work suggests that chloramphenicol may have a much wider application in the treatment of bacterial infections than was once thought likely. Altemeier and Culbertson[11] report that it is valuable against various surgical infections due both to gram-negative bacilli and to gram-positive cocci. Similar trials are briefly recorded by Pulaski,[12] who states that "over 90 per cent of the common surgical organisms (except proteus and *Pseudomonas pyo-*

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[1] Ehrlich, J., Bartz, Q. R., Smith, R. M., Joslyn, D. A., Burkholder, P. R. *Science*, 1947, 106, 417.

[2] Smadel, J. E., Jackson, E. B. *Ibid*, p. 418.

[3] Smith, R. M., Joslyn, D. A., Gruhzit, O. M., McClean, I. W. jun., Penner, M. A., Ehrlich, J. *J. Bact.* 1948, 55, 425.

[4] Smadel, J. E., Leon, A. P., Ley, H. L., Varela, G. *Proc. Soc. exp. Biol., N.Y.* 1948, 68, 12.

[5] Smadel, J. E., Woodward, T. E., Ley, H. L., Philip, C. B, Traub, R., Lewthwaite, R., Savoor, S. R. *Science*, 1948, 108, 160.

[6] Pinkoffs, M. C., Guy, E. G., Lister, L. M., Woodward, T. E., Smadel, J. E. *Ann. intern. Med.* 1948, 29, 656.

[7] Smadel, J. E., Jackson, E. B. *Proc. soc. exp. Biol., N.Y.* 1948, 67, 478.

[8] Wood, E. J. *Lancet*, 1949, ii, 55.

[9] Woodward, T. E., Smadel, J. E., Ley, H. L., Green, R., Mankikar, D. S. *Ann. intern med.* 1948, 29, 131.

[10] Rebstock, M. C., Crooks, H. M. jun., Controulis, J., Bartz, Q. R. *J. Amer. chem. Soc.* 1949, 71, 2458.

[11] Altemeier, W. A., Culbertson, W. R. *J. Amer. med. Ass.* 1951, 145, 449.

[12] Pulaski, E. J. *Ibid*, p. 456.

nea)" are sensitive to chloramphenicol. On another ge of this issue Dr. FLINT and his colleagues describe rial of chloramphenicol locally in the treatment of und infections. These workers recommend the use 5% chloramphenicol. as a powder or, preferably, olution in propylene glycol. This concentration is, course, very high (a 5% solution of penicillin uld contain over 80,000 units per ml.). The fections treated, which were mostly due to *Ps. ocyanea*, *Proteus vulgaris*, and penicillin- and eptomycin-resistant staphylococci, all responded to is local therapy, usually within a few days; and e antibiotic did not appear to delay wound healing, hich in all cases improved after the disappearance bacteria. There was no instance of sensitivity action. Dr. BANKS, also in this issue, recommends loramphenicol for the treatment of penicillin-sistant staphylococcal infection. As a result of cent experience he now regards this antibiotic, ther than aureomycin. as the drug of choice for ich infections, since it is more readily available and heaper, and causes less gastro-intestinal disturbance. NDERSON and ELLIS[13] have likewise indicated that hloramphenicol may be useful in staphylococcal fection. They report the successful treatment of wo cases of penicillin- and streptomycin-resistant taphylococcal meningitis by means of intrathecal njections of chloramphenicol.

FINLAND and his colleagues[14–16] have carefully ompared the effects of seven antibiotics on various acterial species. A notable feature of these investigations is the uniformity of the results with chloramphenicol. Thus among 25 strains of pathogenic staphylococci the minimum bacteriostatic concentration with aureomycin ranged from 1·6 to 6·3 μg. per ml., and with penicillin from 0·08 to 250 μg. per ml.; whereas with chloramphenicol it was 6·3 μg. per ml. for all strains. Most coliform bacilli, other than proteus and *Ps. pyocyanea*, were inhibited by 6·3 μg. of chloramphenicol per ml. Against proteus, this antibiotic gave the best average results of the seven antibiotics tested: but the minimum bacteriostatic concentration with different strains ranged from 3 to 50 μg. per ml. *Ps. pyocyanea* was inhibited only by 100–500 μg. per ml., and a few strains were even more resistant. The "development" of resistance to chloramphenicol has not yet become a problem in this country, although a moderate increase in resistance of a strain of *Salmonella typhi* during chloramphenicol treatment of typhoid fever has been reported from Sheffield.[17] Both ALTEMEIER and CULBERTSON[11] and PULASKI[12] record the emergence of chloramphenicol-resistant strains of staphylococci and gram-negative bacilli in a few cases. Strains of coliform bacilli resistant to[18] and even dependent on[19] chloramphenicol have been isolated in the laboratory. It may, therefore, be only a matter of time and more widespread use of this antibiotic before an increasing number of such strains appear. Clearly, however, their appearance is likely to be much slower than was the case with streptomycin-resistant strains.

If chloramphenicol is to be widely used its toxic effects should be remembered. The most important of these are hæmopoietic changes, including granulopenia and anæmia.[20–22] The action of chloramphenicol on the normal bacterial flora of the body[22] with subsequent development of moniliasis[23–26] is well known. JANBON and BERTRAND[27] have suggested that the anæmia arising during chloramphenicol treatment is associated with alteration in intestinal flora, leading to an upset in enzyme equilibrium of the intestine and inhibition of the anti-anæmic factor. ALTEMEIER and CULBERTSON, however, noted no serious toxic effects and no hæmopoietic changes during the systemic treatment of 179 cases with a daily dose of 25–75 mg. chloramphenicol per kg. body-weight.

These reports seem to warrant a more extended trial of chloramphenicol in the treatment of penicillin-resistant infection. The need for laboratory control of all chemotherapy is, however, becoming increasingly obvious. With the ever-growing incidence of drug-resistant bacteria, even a bacteriological diagnosis is not sufficient guide without sensitivity tests. Chloramphenicol may, as Dr. BANKS suggests, be the antibiotic of choice for the penicillin-resistant staphylococcal infection. It is certainly not so for infections due to penicillin-sensitive staphylococci. Whatever the position may be in hospital practice, in the majority of staphylococcal infections outside hospitals penicillin remains by far the most active chemotherapeutic agent.

The Budget

To check the dangerous drain on our gold reserves the Government are reducing imports and encouraging exports. Failing an equivalent increase in production, the effect must be that we shall have less to buy; and, if we had the same amount to spend, prices would rise because goods would be scarcer than money. To combat this inflationary tendency the Chancellor is adopting the somewhat paradoxical method of raising some prices himself: by reducing the food subsidies from £410 million to £250 million he is putting up the cost of living by perhaps 1*s*. 6*d*. per head per week. This is defensible on the ground that the taxpayer's money should not be spent on all and sundry but rather on those who really need it: and it is compensated by aid to needy groups in the shape of higher retirement allowances and a rise of family allowances from 5*s*. to 8*s*. To revive lost incentives to work, the incidence of income-tax is to be more gradual, and some 2 million people will cease to be liable. On the other hand, by way of disinflation, borrowing will be more expensive, profits taxed more heavily, and contributions to National Insurance higher. Mr. BUTLER thus tries to secure simultaneously lower consumption, harder work, and some equality of sacrifice. But with prices rising, he seems to offer relatively little comfort to families below the present income-tax range, and we wish the increase in family allowances were bigger.

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[13] Anderson, K. F., Ellis, F. G. *Brit. med. J.* 1951, ii, 1067.
[14] Finland, M., Frank, P. F., Wilcox, C. *Amer. J. clin. Path.* 1950, 20, 325.
[15] Frank, P. F., Wilcox, C., Finland, M. *J. Lab. clin. Med.* 1950, 35, 188.
[16] Frank, P. F., Wilcox, C., Finland, M. *Ibid*, p. 205.
[17] Colquhoun, J., Weetch, R. S. *Lancet*, 1950, ii, 621.
[18] Coffey, G. L., Schwab, J. L., Ehrlich, J. *J. infect. Dis.* 1950, 87, 142.
[19] Gocke, T. M., Finland, M. *Proc. Soc. exp. Biol., N.Y.* 1950, 74, 824.
[20] Rich, M. L., Ritterhoff, R. J., Hoffman, R. J. *Ann. intern. Med.* 1950, 33, 1459.
[21] Vollini, I. F., Greenspan, L. Ehrlich, L., Gonner, J. A., Felsenfeld, O., Schwartz, S. O. *J. Amer. med. Ass.* 1950, 142, 1333.
[22] Gray, J. D. *Lancet*, 1950, i, 150.
[23] Mangiaracine, A. *New Engl. J. Med.* 1951, 244, 655.
[24] Harris, H. J. *J. Amer. med. Ass.* 1950, 142, 161.
[25] Tomaszewski, T. *Brit. med. J.* 1951, i, 388.
[26] Woods, J. W., Manning, I. H., Patterson, C. N. *J. Amer. med. Ass.* 1951, 145, 207.
[27] Janbon, M., Bertrand, L. *Bull. Mém. Soc. Méd. Hôp. Paris*, 1951, 67, 999.

Annotations

POLIOMYELITIS: A NEW APPROACH

IMMUNISATION against virus diseases has had its two great successes with smallpox and yellow fever, against each of which living "attenuated" virus is used. In contrast, immunisation with inactivated viruses against such diseases as influenza and mumps has been much less successful. With poliomyelitis, however, both types of approach have been followed.

Morgan[1] has shown that immunisation of monkeys by parenteral inoculation with inactivated poliomyelitis virus produces serum antibody in high titre and some resistance to challenge with virulent virus. There are, however, two serious obstacles to applying this experimental finding to man: first, poliomyelitis virus cannot be readily purified from the normal constituents of nervous tissue, which are known to produce allergic encephalitis; and secondly, as in many fields, there is the difficulty of finding enough animals to produce enough virus for man's demands. On the other hand, the use of a multiplying attenuated virus for immunisation in man is at least feasible. Howe and Bodian[2] have infected chimpanzees by feeding them with poliomyelitis virus; and Melnick and Horstmann[3] have shown that such animals become intestinal carriers, excrete virus in their stools, develop serum antibody, and resist reinfection. In his Herter lectures Burnet[4] said:

> "The logical approach from the ecological angle toward the prevention of poliomyelitis is either to find acceptable means of ensuring a reasonable transfer of intestinal infections between children in infancy or to devise some means of effective immunisation. The technical difficulties of obtaining a dead virus vaccine seem at the present to be insurmountable, and I feel confident that sooner or later it will become necessary to use living vaccines given by mouth in infancy, perhaps under cover of gamma globulin passive protection."

The way to experiments in human immunisation lay open; but who would have the courage to bell the cat?

Koprowski and his associates,[5] in a most important paper, describe the results of feeding live poliomyelitis virus of low virulence to 20 volunteers. The virus which they used was prepared from the brain and spinal cord of cotton-rats infected with a rodent-adapted strain of poliomyelitis virus. In none of the 20 were signs or symptoms of illness noted, despite strict watch for any rise of temperature or evidence of gastro-intestinal or neurological disturbance. Most of the volunteers, however, became intestinal carriers of virus; and all who were not initially immune developed antibodies in their blood to the homologous Lansing type viruses, but not to the heterologous Brunhilde type viruses which seem to be the commonest type isolated at present from cases of poliomyelitis. All interested in poliomyelitis will await further developments of this work with very great interest. But Koprowski and his colleagues are careful to point out that discussion of immunisation by oral administration of poliomyelitis virus is best deferred until this procedure is proved safe. Attenuated organisms of all three immunological types of poliomyelitis virus might be required; and the brilliant work of Enders et al.[6] in growing the virus in tissue cultures may help to furnish this.

Koprowski et al. tell us in a footnote that for obvious reasons the age, sex, and physical status of each volunteer are not mentioned. The reasons must be more obvious to the authors than to the reader, who can only guess, from the methods used for feeding the virus, that t volunteers were very young and that the volunteeri was done by their parents. One of the reasons for th richness of the English language is that the meani of some words is continually changing. Such a word i "volunteer." We may yet read in a scientific journ that an experiment was carried out with twenty volunte mice, and that twenty other mice volunteered as control

ORTHOPÆDIC JUDGMENT

WHEREAS in many other branches of surgery t saving of life must be the paramount concern, the su cess of an orthopædic operation is judged by the exte to which the patient is rid of his pain and relieve of his disability. It is this distinction, said Mr. Phi Wiles in his presidential address to the section of ortl pædics of the Royal Society of Medicine on March that lays upon the orthopædic surgeon a special respon bility when he advises a patient to undergo an operati The surgeon must be particularly confident that t patient will emerge an abler and more comfortable be than before; that his improvement will justify t ordeal; and that the risk of surgery is a reasonable o in the circumstances. The apparently irrational fe of the patient should be respected: it is too oft disastrous to persuade an unwilling person to have operation. Since it is our aim, said Mr. Wiles, to relie symptoms, it is the sufferer who must finally weigh t risk and balance his apprehensions against the probal gain. Moreover, it is easy to say: "Come into hospit and I'll put you right in no time"; but what is t cost to a man and his family? He may have been al to continue work despite, for example, a prolaps intervertebral disc. How often, Mr. Wiles asked l audience, have you seen that same man six or twel months after operation when he was still not back at l old work? For the completely incapacitated the risk m be justified, but who shall judge in other circumstance The right time for operation is when the patient knows t dangers and is willing, and indeed anxious, to face the

But Mr. Wiles thought that the hardest thing of is to give a proper estimate of the benefit which m reasonably be expected from operation. There are many variables: on the one hand, the personality of t patient, his threshold for pain, and his coöperatio on the other, his physical condition and the respon of his tissues to the operation and the subseque reablement. The answer is a guess, though it is a gue which becomes more and more accurate as the experien of the surgeon grows.

Turning to the opportunities for the younger ma Mr. Wiles remarked that, while instruction in the actu techniques of orthopædics is not hard to get, it is no too easy nowadays to acquire the essential basic traini in general surgery. Rapid specialisation has chang the pattern and character of surgery in the last twen or thirty years. "How is the surgeon in training obtain a sufficiently varied experience now that t general surgical wards no longer contain a representati cross-section of surgical practice?" he asked. An "how should the surgical beds of a teaching hospit be divided to give sufficient representation to t specialties and yet maintain a proper balance?" Bot questions could in part be answered, he thought, b giving the specialised surgeon a larger share in th teaching of basic surgery and by allotting him certai of the teaching beds now labelled "general surgery. Thus a student would spend, say, three months of a si months' surgical appointment with a genito-urinary, a orthopædic, or a rectal surgeon, who would use h special cases to illustrate surgical principles. Th number of men who are fitted by training and temper ment for work of this kind is limited, but neverthele Mr. Wiles urged the teaching hospitals to consider mo

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1. Morgan, I. M. *Amer. J. Hyg.* 1948, 48, 394.
2. Howe, H. A., Bodian, D. *J. exp. Med.* 1945, 81, 217.
3. Melnick, J. L., Horstmann, D. M. *Ibid*, 1947, 85, 287.
4. Burnet, F. M. *Bull. Johns Hopk. Hosp.* 1951, 88, 119.
5. Koprowski, H., Jervis, G. A., Norton, T. W. *Amer. J. Hyg.* 1952, 55, 108.
6. Enders, J. F., Weller, T. H., Robbins, F. C. *Science*, 1949, 109, 85.

illy a plan which might be of very great value. In so, he reinforced the arguments of Mr. D. H. in his presidential lecture to the society's section gery last year.[1]

TIMING OF INSULIN

E effect of insulin on carbohydrate metabolism s greatly with the interval before food is taken.[2] r instance, soluble insulin is injected subcutaneously it the same time glucose 100 g. is taken by mouth, elerates glucose assimilation to such an extent that ntary hyperglycæmia is completely suppressed. owever, the insulin precedes the ingestion of glucose ome 40–50 minutes the hypoglycæmia that develops ng this interval stimulates the body's compensatory ianism so effectively that alimentary hyperglycæmia eatly increased, and glucose tolerance is so impaired glycosuria may result even in normal people.[2] In etics the body's reaction to hypoglycæmia is exaggerated, and the diabetes may be greatly accentuated a considerable time. A number of mechanisms icipate in this anti-insulin reaction; and of these release of adrenaline by the adrenal medulla and of xycorticoids by the adrenal cortex stimulated by C.H. are probably the most important. The rôle of naline is illustrated by the greater susceptibility to oglycæmia of diabetics receiving hexamethonium pounds,[3] while the rôle of the adrenal steroids is trated by: (1) patients with rheumatoid arthritis and lin hypoglycæmia, during which uric-acid excretion ncreased and the eosinophil-count falls[4]; and (2) in which the adrenal medulla has been removed, in which the adrenal ascorbic-acid content falls r insulin hypoglycæmia.[5]

he clinical importance of these insulin effects is clear. vould seem wise to recommend the administration of ible insulin within 15 minutes of the next meal. en used alone, delayed-action insulins, and particuy protamine-zinc insulin, need not be so accurately ed in relation to meals. It is well, however, to give oin insulin $^3/_4$–1 hour before a meal, because of the g latent interval before it produces its hypoglycæmic ct.

NTRASPLENIC GRAFTS OF OVA AND OVARIES

CCORDING to a report in the *New York Times* of rch 2, Dr. C. C. Little and his colleagues at the Roscoe Jackson Memorial Laboratory, Bar Harbor, Maine, e obtained normal living young mice from ova transnted into spleens and left for as long as 60 days before ng regrafted into ovaries of foster-mothers. The ung mice so produced showed no hereditary changes at least four generations.

The purpose of this weird experiment must seem scure without some knowledge of its forerunners. eviously M. S. Biskind and G. R. Biskind[6] had grafted mplete ovaries into spleens of ovariectomised rats. ny of the grafts developed into tumours and some etastasised to the liver. The tumours which arise der these conditions are granulosa-celled growths, ecomas, and mixtures of the two. Li and Gardner[7] ve obtained these tumours in all strains of mice which ey have tested; and they revealed the autonomous ture of such neoplasms by successfully transplanting me into intact new hosts in which the tumour cells re no longer subject to unopposed gonadotropin. e tumours produce œstrogen in sufficient amount, or such a character, that it is not inactivated in the liver, r the uteri are larger than those of castrate animals. An essential condition for success in these experiments is bilateral removal of both gonads of the host into whose spleen the new implant is to be made. The Biskinds argued that as the splenic circulation drains into the liver, the hormones carried to it from the grafts will be inactivated. With the hosts' gonads excised no hormones from that source will oppose the production of pituitary gonadotropin, which will be secreted unopposed and will act continuously on the intrasplenic grafts. The tumours which arise provide a clear-cut example of the tumorigenic action of a hormone under exceedingly artificial conditions.

One purpose of the latest experiments thus appears to be to identify the cell of origin of the malignant tumours. Ova, in contrast to ovaries, did not undergo any malignant or other change as judged by the eventual production from them of normal living mice. Thus the origin of the new formations, whether hyperplasias or neoplasias, must lie, as was supposed, in the cells of the graafian follicle when whole ovaries are used. What is not yet known is the length of time that the ovary must remain continuously exposed to gonadotropin, and the total dose required, before malignant changes appear. The first of these problems is being tackled at Bar Harbor.

TRANSFUSION EQUIPMENT

LAST week a committee set up by the International Organisation for Standardisation met in London under the chairmanship of Sir Alan Drury, F.R.S., to discuss the standardisation of transfusion equipment, particularly the modifications that would have to be made in existing types of equipment to bring about functional interchangeability of transfusion sets and containers. France, Norway, Sweden, Denmark, Finland, Holland, and the United Kingdom sent delegates, and New Zealand and India sent observers.

The problems facing the committee were substantial. Since 1945 transfusion services have grown apace and have developed many types of equipment, each of which, in the eyes of its designers, is obviously better than all the others. To have aimed at international agreement on one pattern of equipment would have been illusory; but it was also unnecessary, provided agreement could be reached on certain general principles.

The first problem tackled was that of glass transfusion containers, the essential dimension of which, as regards interchangeability, is the internal neck diameter. It appears that the two most widely used containers have internal neck diameters of 22·5 mm. and 30 mm., and the recommendation was made that transfusion services should adopt either the one or the other. The former type of container is already widely used, the transfusion services of the U.K., Scandinavia, Holland, Belgium, Australia, Canada, and other countries having adopted it. The 30 mm. bottle is the only bottle for intravenous fluids permitted by law in France, and it is also used to some extent in the U.S.A. Unfortunately the U.S.A. did not send a representative; so the committee had no first-hand information.

The committee then agreed on the general characteristics of the closures to be used for these two containers, and went on to discuss the design of piercing needles, with which transfusion sets should be equipped. Agreement was reached on the essential dimensions of the hubs of such needles, with the result that a general recommendation could be made on the internal diameter of tubing and the dimensions of those parts of the filter chamber, drip-counter, and needle mounts to which the tubing is attached. The committee also decided on a specification for the performance of filters.

The immediate and most important result, if these recommendations were incorporated in national standards, would be that with any transfusion set (which would be equipped with piercing needles to perforate the rubber closure of the transfusion bottle) one could use any bottle of blood or plasma; in other words, functional interchangeability would be brought about. Secondly, many of the components of the transfusion set would be internationally interchangeable. But two components

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Lancet, 1951, ii, 875.

Somogyi, M. *J. biol. Chem.* 1951, 193, 859.

Laurence, D. R., Stacey, R. S. *Lancet*, 1951, ii, 1145.

Kersley, G. D., Mandel, L., Jeffrey, M. R., Desmarais, M. H. L., Bene, E. *Brit. med. J.* 1950, ii, 855.

Vogt, M. *J. Physiol.* 1951, 114, 222.

Biskind, M. S., Biskind, G. R. *Proc. Soc. exp. Biol., N.Y.* 1944, 55, 176; *Ibid.* 1945, 59, 4; *Cancer Res.* 1950, 10, 309.

Li, M. H., Gardner, W. U. *Cancer Res.* 1949, 9, 35.

—the bottles and needles—will not be internationally interchangeable. Unless one took the precaution of having closures to fit both types of container, one could not, in an emergency, make continued use of both types of bottle, though one could extract their contents; nor could one make use of the needles used for intravenous injection, for it seems that there may always be Luer, Record, and, in France, Pravaz fittings. The committee did recommend, however, with only one dissentient, that the Luer fitting be adopted.

Having got its teeth into the problem, the committee set up working groups on the performance standards of glass for the bottles; on the over-all dimensions of the 22·5 mm. bottle, which is at present made in various shapes; and on the type of fitting to be used for needles.

GENETICS AND MEDICINE

Prof. Maurice Lamy, of Paris, is remarkable in that he is a pædiatrician who also holds a chair of medical genetics. At the Institut Français in London, on Feb. 12, he outlined the history of human genetics and indicated some of the implications of genetics for medicine, education, and the treatment of crime.

Man is a difficult subject for genetic study; he has small families and a long life, and he does not marry to suit the geneticist. But statistical and biometrical methods to overcome these difficulties have been developed from the pioneer work of Francis Galton. In particular, Galton originated the valuable method of the comparison of twins. Pathological processes may be divided into three groups: those entirely due to environmental factors, such as trauma; those entirely due to genetic factors, such as hæmophilia; and those where factors both of nature and nurture are responsible—for example, diabetes. This last is by far the largest and most interesting group Twin studies are often the best way of correctly assigning a particular pathological process to one of these three classes; for example, tuberculosis and recidivism have been assigned to the third class in this way. The tasks ahead of medical genetics are: to catalogue the diseases which are genetically determined; to establish their mode of inheritance; to determine their frequencies; and to find means of detecting "carriers." These studies are not mere academic exercises. Real prophylaxis of disease will depend in most instances on the detection of those people who are genetically predisposed to it; only then will it be possible to apply the appropriate special methods of environmental care to the individual child economically and effectively. The art of genetic prediction—that is, the estimation of the chances that any particular mating will result in children with genetically determined malformation or disease or predisposition to these—is becoming increasingly accurate. Even now Professor Lamy is often consulted by young people wishing to marry but worried about some ill health in the family. Often he can reassure them by explaining that the chances of their children being affected are small; sometimes he has to advise against marriage, though this advice is not always taken.

In the future, Professor Lamy added, the State will have to give much thought to the applications of human genetics. Compulsory sterilisation is ineffective, for it is based on bad philosophy and bad genetics. But a certain amount of control over marriage may be necessary; a considerable reduction in the frequency of many recessively determined conditions would be quickly achieved if cousin marriages were forbidden. How far the State should interfere and forbid marriages on eugenic grounds is for future generations to decide; a compromise must be found between the claims of health and of liberty. It is most desirable, however, that a knowledge of the principles of human genetics should be spread widely

LEONARDO THE ANATOMIST

THE exhibition which the Royal Academy is holding at Burlington House to celebrate the quincentenary of Leonardo da Vinci's birth, contains, besides a selection of his drawings and copies of his paintings by his pupils a scientific exhibit. A series of drawings and models, arranged by the Science Museum, illustrates the extraordinary ingenuity and resource which this remarkable man brought to the solution of scientific and engineering problems. Many of his ideas remained buried in his notebooks for three hundred years. As Dr. Charles Singer wrote, "his private papers contain evidence not only of a unique scientific insight, but of an industry which is almost incredible." Though he drew like an angel, he wrote like a peasant and his manuscripts are covered with mirror-writing and peculiar abbreviations which for many generations effectively concealed their mighty secrets.

The medical visitor will find a delightful professional interest in the anatomical studies. Here the Science Museum sought the help of Dr. K. D. Keele in selecting and arranging the drawings, some of which are originals and some reproductions. Almost all Leonardo's existing manuscripts are in the Royal Library at Windsor, and King George VI had generously permitted the loan of them for this exhibition.

Leonardo, when he began his anatomical work in Milan, wrote, "I have dissected more than ten bodies for the purpose of getting full knowledge about the veins, destroying all other organs, consuming even to the very minutest particles all the flesh which surrounded these veins." In these dissections he made several important observations. His first studies did not contradict the traditional errors which had been handed down from the days of Galen 1300 years earlier: for example, the early drawings depict a heart of only two chambers and the inferior and superior vena cava as one vessel, giving a branch to the heart. But many years later he drew a four-chambered heart with "upper" and "lower" ventricles and the superior and inferior venæ cavæ as individual vessels, each entering the right "upper ventricle." He did not, as has sometimes been suggested, anticipate Harvey's great discovery, for he held that the blood was tossed to and fro in the ventricles, thus generating heat for the body.

Several examples of his marvellous ingenuity in the investigation of anatomical problems are shown in these drawings. To understand better the nature of the cardiac movement, he transfixed the heart of a pig and noted the different positions of the "piercer" in systole and diastole. He also described a method for making a cast of the aorta to study the flow of blood through the aortic valve. He filled the ventricles of the brain with wax and when the wax had set he dissected it out and made, for the first time, accurate drawings of the ventricles. Dr. Keele nicely comments on the accuracy of these representations by setting against them a modern encephalogram. In the same way Leonardo's dissection of the femoral vessels is compared with a femoral arteriogram.

By a skilful selection, Dr. Keele has displayed most of the original observations made by Leonardo. He has also written a good introduction and provided admirable notes for each drawing. The exhibition is to remain open for three months. On April 24 Dr. Keele is to lecture on Leonardo's Research on the Heart and the Blood, and on May 29 Dr. Charles Singer on Leonardo and the Structure and Action of the Human Body. In this exhibition art and science find a rare meeting-place.

DR. C. KILLICK MILLARD, formerly medical officer of health for Leicester, and founder of the Voluntary Euthanasia Legislation Society, died on March 7, at the age of 81.

OWING to the illness of one of the General Medical Services Committee's leading counsel, with the agreement of both parties and the concurrence of Mr. Justice Danckwerts the hearing of the adjudication has been postponed until Tuesday, March 18.

Special Articles

.CTS AND FIGURES ON ALCOHOLISM*

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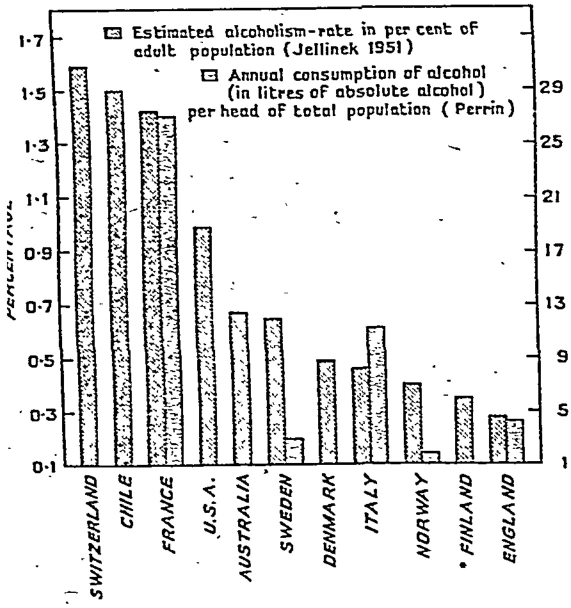
ISLEWORTH

HY do people drink to excess? We know little ut the cause of alcoholic addiction.

n itself, it is the most natural thing in the world to to alcohol, and some of us, the fortunate ones, can do ; with impunity. But there is a minority of people) cannot, and in time alcohol becomes their master. ne believe that these people become slaves to alcohol ause of their physiological make-up; others believe t this happens because of their psychological make-up.

Alcoholism affects all nations and all classes of the nmunity; the man-in-the-street as much as the idle h—or perhaps more, because he has no line of retreat— t it has always been difficult to assess the number of oholics in a country, and such figures have been reliable.

Of late, under the guidance of Jellinek, an expert mmittee of the World Health Organisation (Jellinek 51) have tackled this problem, and their estimate of the number of severe alcoholic cases in each country is shown in fig. 1. It will be seen that Switzerland is at the top of the scale with 1·6%, while England is at the bottom with 0·28%; Italy, Norway, and Finland are near the bottom; France and the U.S.A. nearer the top.



* Annual consumption of alcohol 0·9 litre.

Fig. 1—Alcoholism-rates for 11 countries compared with annual alcohol consumption in 6 of these countries.

Why is alcoholism more prevalent in some countries than in others? Can this depend on the consumption of alcohol in that country? Before going into this, let us consider outside factors.

CLIMATE

Some 250 years ago Montesquieu (1689–1755) suggested that alcoholism increases from the Equator over the face of the earth in proportion to the humidity of the climate (Baer 1899). Bowditch (1872), who undertook climatic investigations in America, formulated a "cosmic law of alcoholism," according to which alcoholism spreads from the Equator—where there is little—in ever-increasing intensity with the degree of latitude. He maintained that not only the volume of alcoholism increases with latitude but also its virulence; that is, the effects of alcohol on individual and society become more pernicious the further one goes from the Equator.

Another American, Clarence Mills (1946), maintains that energy and driving force of nations is lowest in southern and highest in northern regions. In warmer regions where human energy is low, alcohol produces only a mild excitement which quickly passes into lethargy, while with energetic people of cooler lands the excitement is stronger and often leads to violence.

With southern people, Mills points out, few inhibitions are needed since they act almost as freely when sober as when under the releasing effect of alcohol. On the other hand, inhibitions are socially necessary with the dynamic residents of cooler climates. It is not merely chance, he says, that the temperance movement is largely restricted to northern regions. There may be a good deal in this, when we come to think that in Sweden, for instance, there are: a Union of Temperance Drivers; a League of Temperance Advocates; a Union of Temperance Policemen; a Union of Temperance Students; a Union of Temperance Railwaymen; the Temperance Union of Teachers; and the Temperance Organisation of the Royal Swedish Airforce. Sweden even boasted, at any rate in 1935, a postal correspondence course on alcoholism, by which subscribers (of whom there were 2000) were instructed how to avoid the pitfalls of alcohol.

RACE

There is such a thing as a constitutionally good head or bad head for alcohol. Martensen-Larsen (1950) speaks of an individual threshold, and he found that many of his patients were handicapped by a low threshold—i.e., once they started drinking, they soon developed a craving for more and had to go on drinking. He has noticed that professional men and merchants seem to have better heads for alcohol than labourers and small tradesmen. Here, as almost everywhere in the study of alcoholism, those awkward twins *propter hoc* and *post hoc* play a game of hide-and-seek at our expense: it is hard to know what is the cause and what the effect.

Not only individuals, but whole nations or races have better heads for alcohol than others. At the top of the scale come the Irish, who are notoriously prone to pathological alcoholism; at the bottom comes the Jewish race, in which alcoholism is remarkably low. Next to the Jewish race come the Italians, who, despite a high national consumption of alcohol, have a low

ADMISSIONS FOR ALCOHOLISM AND ALCOHOL PSYCHOSES TO MENTAL HOSPITALS IN U.S.A., ACCORDING TO COUNTRY OF ORIGIN

Country of origin	Rate per 100,000 population of same national origin			Percentage of total admissions of same national origin		
	Alcoholism		Alcohol psychoses	Alcoholism		Alcohol psychoses
	New York City 1930	U.S.A. 1922	New York State 1943–44	New York State 1930	Mass. 1900	New York City 1908
Ireland	22·8	17·1	24·0	11·5	37·0	27·7
Poland	12·0	6·3	11·0			
Italy	4·1	4·3	5·5	..	..	..
Russia	1·9	4·6	2·5	3·1	..	7·7
Jewish	..	..	..	0·4	0·5	0·3

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*From a lecture delivered to the W.H.O. conference on alcoholism at Copenhagen on Oct. 26, 1951.

alcoholism-rate. The Finns, on the other hand, seem to have a bad head for alcohol. Verkko (1948), surveying the effect of drink on crimes of violence in Finland between 1754 and 1944, reaches the conclusion that his fellow countrymen react to alcohol in an unfortunate way.

From American sources (Emerson 1932) I have compiled the table, which shows the rate of pathological alcoholism among people of foreign extraction living in the United States. Even though established in another country, these people still show national or racial propensities. The Irish are consistently at the top of the scale, while Jews are at the very bottom. Pathological alcoholism among Italians and Russians is low, while among the Poles it is fairly high.

Figures for alcohol consumption must be taken with a grain of salt. Inevitably they are only approximate, but the figures (fig. 1) given by Perrin (1950) appear sufficiently reliable for our purpose. Only 6 countries out of the 11 on Jellinek's scale are given by Perrin.

In Italy alcohol consumption overshoots the incidence of pathological alcoholism; we may regard this country as having a good head for alcohol. In France and England alcohol consumption corresponds with the incidence of pathological alcoholism; these countries appear to have a normal head for alcohol. On the other hand, in the United States,† Sweden, Norway, and Finland alcohol consumption undershoots the incidence of pathological alcoholism; so these countries may be regarded as having a bad head for alcohol.

SEX

Alcoholism is much more prevalent in men than in women; in England and the United States, there is 1 woman alcoholic to about 7 men. What are the reasons for this discrepancy?

Some appear obvious, others less so. In the first place, since this is a man-made world, women not only have less opportunities for getting drunk but are frowned upon if they do. No-one really thinks less of a man if he drinks, but with a woman it is different. In the words of the Russian proverb: "If the husband drinks, half the house is aflame; if the wife drinks, the whole house is on fire."

Social censure goes a long way to keep down female alcoholism, but there must be other reasons. The wear and tear of modern life affects woman as much as man; all said and done, women have as much cause, or more, to seek escape in alcohol. However, they don't, or not to the same extent. Possibly the physiological make-up of woman plays a part here, or more probably her psychological make-up; she may have less need to fly to alcohol since she is the stronger sex.

If social censure were the sole reason, one would expect female alcoholism to have risen considerably during the last 40–50 years with woman's emancipation. The world has become more sensible in many ways; social censure is not what it was, and woman is no longer always on the defensive.

Contrary to expectation, alcoholism among women has not increased with their emancipation. Jellinek (1947) surveyed the trends of alcoholism during the last 40 years in the United States, where woman is freer than in any other country, and found that female alcoholism has remained below pre-Prohibition levels. The alcoholic woman has come more into the public view than formerly, but the number of women alcoholics has not increased.

A good deal of what I have said about alcoholism among women applies also to the Jewish race. This is not only a man-made, but also a gentile world. Not so long ago, Jews could no more afford to get drunk than women. But there is more than that in the remarkably low incidence of pathological alcoholism among the Jewish race—all the more remarkable since Jews are prone neuroses.

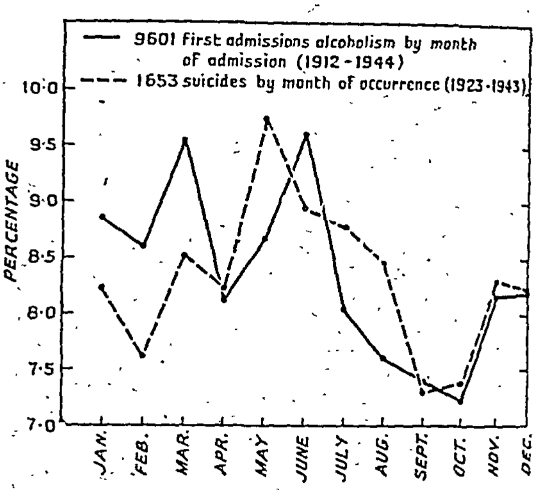

Fig. 2—Seasonal variations for alcoholism and suicide in Switzerl (Lauterburg 1945).

The extremes of alcoholism and of abstinence are ra in Jewish life. One wonders whether their close-kn family ties, their dietary restrictions, or their religio habits—the Old Testament is full of prohibitions again drink—account for this. It would be interesting compare alcoholism among orthodox and non-orthod Jews.

SEASON

Apart from festivals, such as Christmas, is drinki more prevalent at certain times of the year than others?

Let us start by considering the seasonal variations suicide; for suicide, which brings permanent oblivio and drunkenness, which brings temporary oblivio may have something in common. All the world ov suicide-rates show a peak in the spring and are at th lowest during the dark winter months (Swinscow 195 and Lauterburg (1945) finds a comparable cycle f alcoholism (fig. 2). Comparing the monthly distributi of 1653 suicides in Zürich during 1923–43 with that 9601 first admissions to institutions for the alcoholic the same city during 1912–44 he shows that the peak suicide falls in May and the peak of alcoholic admissio in June; also that suicide is at its lowest in Septembe alcoholic admissions in October. In the wintry mont of December suicides and alcoholic admissions are at th same level.

Alcohol psychoses also seem to show a seasonal tren Figures are necessarily smaller here; and the time-la between excessive drinking and the advent of an alcoh psychosis lessens their significance. According to Mälzbe (1947), who recorded the month of admission of 67 alcohol psychotics to New York State mental hospita during 1943–44, the seasonal trend of alcohol psychose is much the same as the trend of admissions for alco holism. The incidence of alcohol psychoses was highes in July, and the admissions for alcoholism were highes in June, while for both groups the lowest incidenc was in October. The greatest difference was betwee the March and September figures; in New York th September figure (10·7%) was the highest but one, i Switzerland (7·4%) the lowest but one.

RETROSPECT

Over 3000 years ago (1400 B.C.) in India, chroni alcoholism and even delirium tremens was known an described in the ancient medical system known a Ayurveda (Ravi Varma 1950).

Almost 3000 years ago (900 B.C.), Lycurgus, a king o Sparta, took up the fight against alcoholism, decreeing vineyards be destroyed and the legs of drunkards be ut off.

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† The annual alcohol consumption was 7·9 litres in 1945 (Jellinek 1947).

Nearly 2000 years ago, the Roman lawyer Ulpian A.D. 170–228) urged that alcoholics should be treated s sick people. But it took centuries for this sensible iew to gain ground, and it was not until 1860 that the rst inebriates' institution in the world was founded in merica, by Joseph Turner.

A great deal of headway has been made since. But espite many sincere and determined efforts, such as Prohibition, no country has yet succeeded in working ut a solution of the problem. A vast amount of human appiness and misery is at stake, and we must never orget that alcoholism is not intemperance but a serious affliction. Its victims look to us for help, and whether we are doctors or laymen it is up to us to give it.

REFERENCES

Baer, A. (1899) *Berl. klin. Wschr.* 36, 801.
Bowditch, H. J. (1872) *Rep. Mass. Bd Hlth.*
Emerson, H. (1932) Alcohol and Man. New York.
Jellinek, E. M. (1947) *Quart. J. Stud. Alcohol*, 8, 1.
— (1951) *W.H.O. tech. Rep. Ser.* no. 42, p. 19.
Lauterburg, F. (1945) *Gesundh. Wohlf.* 5, 232.
Malzberg, B. (1947) *Quart. J. Stud. Alcohol*, 8, 274.
Martensen-Larsen, O. (1950) *Brit. J. Addict.* 47, 43.
Mills, C. A. (1946) Climate Makes the Man. London.
Perrin, P. (1950) L'Alcoolisme. Paris.
Ravi Varma, L. A. (1950) *Quart. J. Stud. Alcohol*, 11, 484.
Swinscow, D. (1951) *Brit. med. J.* i, 1417.
Verkko, K. (1948) *Manniska och Miljo, Helsinki*, 3, 83.

ISONICOTINIC ACID DERIVATIVES IN THE TREATMENT OF TUBERCULOSIS

FROM A CORRESPONDENT IN CHICAGO

ON March 5, at a joint session of the Chicago Tuberculosis Society and the Tuberculosis Institute, an account of the use of isonicotinic acid derivatives in the treatment of human tuberculosis was given by Dr. **EDWARD H. ROBITZEK**, of Sea View Hospital, Staten Island, New York City.

Dr. Robitzek spoke of the work of Domagk and Behnisch in relation to experimental tuberculosis, especially in the use of semicarbazone drugs, and referred to Cori's use of nicotinic acid in human tuberculosis. Three useful compounds of isonicotinic acid, he said, have now been used in man; and they were found as a result of screening some 5000 thiosemicarbazones, synthesised mainly by H. H. Fox In all, 67 hydrazides of nicotinic acid were tested, and of these a glucosyl derivative proved extremely effective in experimental tuberculosis in mice.

Last May this glucosyl derivative of isonicotinic acid hydrazide was tested by Dr. Robitzek and his colleagues in 5 patients with tuberculosis. Metabolic studies and various types of function tests revealed no abnormalities of function. Unfortunately, the glucosyl derivative was not stable and it was rather difficult to administer. In October clinical trial was started with 17 patients using isonicotinic acid hydrazide. At first the dose was 2 mg. per kg. body-weight, but this was later increased to 10 mg. per kg. The isopropyl derivative of isonicotinic acid hydrazide was synthesised later in the year and has been in use, at a dose of 8 mg. per kg., since January. These drugs are given by mouth.

The patients for this study were carefully selected. All of them had previously had large doses of *p*-aminosalicylic acid or streptomycin, or both, and many had had surgical treatment; but all the chest cases still had positive sputa and bilateral cavitation. Originally 143 patients were chosen, but after re-evaluation by an impartial group 92 of these were selected for testing of the drug. None of them were "terminal" but all were seriously ill. Soon after therapy was started, they began to feel better. Then the dietitians reported that they were demanding more food, and soon it was observed that their sputa and cough had decreased remarkably. Objective evidence for this latter statement was a sharp drop in antitussic drugs supplied to the patients from the Sea View Hospital pharmacy. At this time the temperature returned to normal, and soon there was an increase in weight and a remarkable increase in energy. The nurses reported that the patients' skin was much improved, with return of normal elasticity. Of the 92 patients, 25% had persistent negative sputa and negative gastric washings; in 28% the sputa and gastric washings became very occasionally positive; and in the remainder there has been a marked decrease in the amount of sputum and cough, though cultures are still positive.

The X-ray changes were not as striking as the changes in body-weight and general condition. In 2 patients cavities were completely closed, and in 33 there was a marked reduction in the size of the cavity with loss of fluid levels. There were 14 patients with huge cavities and negative sputa. In many of the patients, there was tuberculous involvement of the larynx, tongue, ear, joints, and bones; and many with bone tuberculosis had draining sinuses. The 10 with laryngeal involvement all benefited: pain has gone, they can now swallow, and healing has been observed by the laryngologists. Of 2 patients with tuberculous otitis, the condition has completely healed in one, and in the other drainage has been cut and hearing has been restored. In the orthopædic patients, many of whom had had as much as 1200 g. of streptomycin, all superficial lesions are closed and the majority of deep lesions have improved.

Dr. Robitzek then presented some case-histories illustrating the rapid fall of temperature and gain in weight. In a patient with a temperature of 102° and 103°F there was a rapid return to normal in twenty-four hours, and the chart looked like that of a patient with pneumonia terminating by crisis. The average gain in weight of all patients was 2·4 lb. per week for a period of twelve weeks. The weight of one of them rose from 111 lb. to 196 lb. in ten weeks. Radiographs of the 2 patients whose cavities have healed completely were impressive, but less impressive than those of a patient with bilateral cavities (one as big as a coconut) in which sputa and gastric washings were now negative. This patient has regained 40 lb. in weight, and the temperature returned to normal within three days of beginning treatment. A huge tuberculous ulcer extending over the anterior half of the tongue healed completely with therapy. Three draining sinuses (one from a spine, one from an ankle, and one from the bones of the hand) closed completely and have remained closed.

Dr. Robitzek took a very conservative attitude towards his observations. He said that "there is much work and research to be done on the drugs before one can determine their real value." He believes that it will be at least six months before the true value of the new drugs is known.

Medicine and the Law

Blood in the Wrong Refrigerator

AT an inquest at Hammersmith on Feb. 21, the death of a 23-year-old man was attributed to transfusion with blood which had been hæmolysed by storage at too low a temperature.[1] The blood had been accidentally placed in a refrigerator used for bone grafts and kept at a temperature of –8°F. Red cells are normally hæmolysed by temperatures only slightly below freezing-point. A verdict of misadventure was recorded.

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[1] *Manchester Guardian*, Feb. 22, 1952.

Public Health

DIPHTHERIA CARRIER INVESTIGATION

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From the University of Leeds and the City of Leeds Health and Education Departments

WE have for some time suspected that the diphtheria carrier-rate in Leeds had become very low. The point seemed of particular interest since a high level of immunisation has been maintained among Leeds children for some ten years. A joint arrangement was therefore made between the Departments of Preventive Medicine and Public Health, and of Bacteriology, of the University of Leeds, and the Health and Education Departments of the City of Leeds, for a sample of schoolchildren to be examined for the presence of diphtheria carriers.

The selection of the children, swabbing, documentation, and analysis was done by the Department of Preventive Medicine of the University of Leeds and the City of Leeds Health and Education Departments, and the swabs were examined by the Department of Bacteriology.

METHODS AND MATERIAL

A small pilot survey was undertaken in June and July, 1950, to test the laboratory technique for the examination of considerable numbers of swabs.

The swabs were plated out immediately on arrival in the laboratory, using a slight modification of the medium described by Johnstone and Zinnemann (1943). The blood used in this medium was laked by freezing and thawing, and the sodium tellurite solution was added at once, before the plates were poured.

On the field side one person with considerable experience in survey work took all the swabs, in each case one from the throat and one from each nostril, and trained clerical staff filled in details of age, sex, occupation of parent, and details of history, tonsillectomy, diphtheria, and immunisation. For field investigations of this kind to succeed, disorganisation of the school should be minimal, and the whole procedure must therefore be done as quickly as possible.

For the pilot period the swabs were taken daily, but it was found impracticable to proceed in this way, and swabbing was altered to one day a week with a larger number of children. 100 children were swabbed each week, three swabs from each, and it was possible to complete between 9.15 A.M. and 11.30 A.M. Subsequently the number was reduced to 75 because this could be completed before the lunch break with less effect on the school work. The only differences in the laboratory technique between the pilot experiment and the main series was the incorporation of 1% liq. 'Tripsin' co. (Allen & Hanburys) in the medium to improve its growth-promoting qualities (Gordon and Zinnemann 1949); and, to economise in the use of medium, the three swabs from each child were inoculated on to a quarter of the surface of a plate. As this method makes it impossible to determine the source (nose or throat) of the organism, any possible carriers were reinvestigated and the swabs plated out separately.

The schools were selected, so far as possible, to give an even distribution of sex, ages between years 5 and 15, and social classes. A record card of the dual-purpose type was made for each child for Powers-Samas analysis, space being provided on the card for the recording of further bacteriological investigations on any strains which might be isolated and on ot organisms present in the throat or nose. From Ju 1950, to June, 1951, about 2100 children were swab and from November to December, 1951, a further s The initial 2100 have been analysed into age, sex, a social class, the last being determined by quest the children—a matter of some difficulty with t younger ones.

Comparison of the sample with the total sch population in Leeds shows that the division into mal and females is representative. The division into differe ages between 5 years and 15 shows that the sample i slightly deficient in ages 5, 6, and 8–10 years and has slight surplus of children between 10 and 14. It ca however, be said that the sample contains a fair representative number at each age. Comparison o social class suggests that the sample contains a slightl higher proportion of children in social class 3 and than is present in the Leeds population, but this ma well be explained by the tendency to overgrade th social class on the information supplied by the childre

RESULTS

From the 6300 swabs examined by the end of la June, five strains of *Corynebacterium diphtheriæ* wer isolated. Morphologically, by colony appearances, b growth in broth, and biochemically, these five strain were of the mitis type, but all proved non-pathogeni to guineapigs weighing 350 g. The 375 swabs obtaine between June and December have not yet been analyse according to age and social class, but they too show n carriers.

This result is from a series of nose and throat swab all taken by the same experienced person and examine in a laboratory highly experienced in the examinatio of this type of material. During this period 3 cases o diphtheria in children aged 5–15 years occurred in th City of Leeds (total population 500,000) with a school child population of about 66,000.

Analysis of the immunisation state of the childre in the sample showed that 91·4% had been immunise against diphtheria; and boosting doses had been give to 77% of those aged 10–15 years, 58% of those age 6–9 years, and 12·3% of those aged 5–6 years. Th sample is of a highly immunised child community, an the incidence of the disease during this period has bee extremely low.

COMMENTS

Discussion of the important implications of thes findings is left until further data are available. Th investigations are continuing weekly, particular atten tion being paid to organisational details so as to caus the least inconvenience to the schools. It is intende to continue the survey for some years, so as to determin any change in the carrier-rate and to correlate this with the incidence of diphtheria and the percentage of children immunised.

It is felt that these preliminary results are of considerable interest, and that similar surveys in other areas in Great Britain would be of value.

REFERENCES

Gordon, M., Zinnemann, K. (1949) *J. clin. Path.* 2, 209.
Johnstone, K. I., Zinnemann, K. (1943) *J. Path. Bact.* 55, 53.

Variola Minor in Lancashire

At the beginning of March there was a flurry of cases in the Lancashire outbreak of variola minor; in the week ended March 8 notifications numbered 62, bringing the total since the start of the outbreak to 88. Since then, however, the incidence has fallen. The disease is confined to Rochdale apart from a few patients resident in neighbouring districts who were infected in Rochdale. Such cases have been notified from Milnrow, Heywood, and Littleborough, where the first case has been recognised in an unvaccinated child. There have been no deaths. The diagnosis of variola minor is now certain.

In England Now

Running Commentary by Peripatetic Correspondents

N the rapidly expanding field of occupational disease, le attention, and that only superficial, has been paid humeral buzzing. A recent report from Barnes Hall 52) is the first published study in this country.

n the present state of medical nomenclature I hesitate make confusion worse confounded, but it seems eferable to avoid a name which relates to the main n of the disease and takes no account of the true cause.

Originally, it was believed that the position of the ll-push was responsible for this baffling malady among turers. That this is not so has been demonstrated a striking series of experiments carried out by the anufacturers of the apparatus (Messrs. Pritchard & Co., rsonal communication, 1952). Various positions of e push were tried and a careful note kept of results.

pear-shaped switch on a dangling cord appeared omising but failed through the action of a visiting turer, who, under the impression that the fitting as his key chain, detached it en bloc from the desk, it it in his trouser pocket, and endeavoured to distract tention by accusing the lantern operator of showing s slides upside down.

A return was made to the original bell-push, but is was now fitted under the ledge of the desk. This periment had in turn to be abandoned after a succession lectures by a long run of desk-edge-grippers. The st of these, indeed, got his forefinger so firmly wedged the bell-push that he could not be released until me hours after the end of the meeting. It was felt erefore that, for the safety of both the lecturer and e bell-push, a suitable position must be found for the ontrol on top of the lecturer's desk.

At this point it became evident that the root of the rouble was not in the position of the bell-push.

A series of positions advancing from rear to fore dge of the desk failed to find any point out of human lbow-reach. A series of infra-red photographs taken ithout the subject's knowledge revealed a tendency to which no exception was found in a series of 500 ases) for lecturers to lean further and further forward ntil at some point an inevitable alarm reaction followed nd the classic clinical picture of the disease became pparent.

The position of the lecturer is therefore the all-mportant factor in this condition; for which I suggest he more accurate title of "Lecturer's declination."

So far the malady has resisted all therapeutic measures. ufferers may find some consolation in the fact that t appears to be non-fatal. Though no complete follow-up tudy has yet been made, it seems probable that the isease is self-limited; at some point the lecturer's orward deviation from the vertical ("lecturer's declination"—to be referred to as L.D. in future communications) must be arrested by his forehead coming into sharp contact with the fore-edge of the desk. Indeed, that may, in many cases, be the happiest possible ending.

* * *

Having battled through my first year in general practice with what, to the onlooker, might have seemed flying colours, I had, to my dismay, joined the ranks of the secret sufferers from dyspepsia. Visits to the alkali box in the surgery had become ever more frequent and furtive. The next stage was the breaking up of mealtime happiness, owing to the need for a fish diet, which on many occasions was forced on all other members of the family.

All this came about because I was afraid I might get an ulcer. This fear became an obsession. This obsession tended to cast a shadow over the family social life, since visits to friends and restaurants were spoiled. The trouble was not the pain or discomfort due to dyspepsia, but fear of the consequences.

The turning-point came at a postgraduate course two years ago, when I listened to a delightful account of the blessings of gastrectomy. I said to myself "It seems that if I could only get a large enough ulcer I could have a gastrectomy, and get rid of these symptoms once and for all." From that day Continental cooking returned to the home. Any dyspepsia due to pickles, wines, fried foods, &c., is now extremely well tolerated. Indeed, if any of your dyspeptic readers have spare jars of well-matured gherkins which they are afraid to use, I should be glad to pay top market prices for them.

* * *

The magistrate had ordered a post-mortem examination. The doctor friend with whom I was staying, right in the wilds—no telephone, gas, or electricity; water fetched weekly—asked if I would like to do it and explained that his post-mortem "set" had been lost in the recent hurricane but he would take some "instruments" with him. So after a drive of ten or twelve miles we reached the scene of operations. The deceased, a coloured man of 28, had died the previous evening, after two days' illness in which he had not seen a doctor. The police had already laid out the body, on a board supported on trestles, in the tiny living-room of the miserable two-roomed wattle-and-daub shack where the man had lived with his wife and two small children. I should have preferred to make the examination in the open air, but the joiner and his assistants were already busy making the coffin outside, and a number of neighbours with their families had arrived, anxious to see what was going on. The walls of the shack were full of holes—in places there were more holes than wall—and the deceased's children kept their eyes glued to suitable apertures throughout the proceedings.

My colleague produced his "instruments," which proved to be a small scalpel, with a $1^{1}/_{2}$ inch blade, and two pairs of clip forceps. With this tiny knife I opened the body and removed and cut up all the organs. There was a hæmorrhagic bronchopneumonia involving the bases of the upper and lower lobes of each lung. Nevertheless, since this was a medicolegal case, I decided to examine the brain, so I sent my colleague to borrow a saw from the coffin-maker. It was the usual joiner's type of saw, with a 30-inch blade which fortunately was fairly sharp. With this instrument I managed to cut round the skull, unintentionally lubricating the saw with the sweat of my brow (it was early afternoon and the heat was intense). To prise off the skull-cap I borrowed a machete (a kind of cutlass) from one of the labourers assisting in making the coffin. However, after all this the brain showed nothing of note.

Then came the "stitching-up." It was suggested that this should be left to the widow, since our policeman assistant did not know how to do it, but that was too much for me. By great good luck I obtained a sacking-needle and string, and having given the constable a demonstration, I left him to finish the job. My colleague and I returned home more than ready for our tea. The coroner's verdict, in a land where murders, including poisonings, are common occurrences, was "Natural causes." Everybody breathed freely once more.

* * *

First-aiders are rightly taught to approach the scene of an accident cautiously, and in competitions the experienced team captain always asks the judge "Is there any further danger?" as one of his first questions. The question was put to me rather dramatically at a recent competition in Yorkshire.

Each team was told that they were watching a circus, and were called on to render first-aid to the lion-tamer, who had been mauled by one of his less docile charges. At the time of the test the casualty had reached the first-aid room, which was set up on a stage, suitably screened from the team and audience. The briefing was done at the foot of a small flight of steps on one side of the stage, and at a given signal the curtains were drawn aside and the first-aiders had to "act as in real life."

Most teams charged up the steps shouting, "All right old chap, we're first-aiders, you'll be all right"; and got to work with commendable speed. One cautious Yorkshireman, remembering his training and perhaps also the sad fate of Albert at the Zoo, stood with outstretched hands barring the assault of his team upon the scene. "Won minute, Doctor," he said anxiously: "wheer's lion now?"

Letters to the Editor

DRUG RESISTANCE OF MICRO-ORGANISMS

SIR,—According to your report (Feb. 23) of the discussion at the Royal Society of Medicine, Dr. J. Ungar asked what should be done with regard to penicillin-resistant staphylococci. This, he declared, was a question of major practical importance. I agree. Dr. Mary Barber and others have shown that the percentage of strains of *Staphylococcus pyogenes* which are resistant to penicillin has greatly increased, at any rate among patients and staff in hospitals. She reported 14% resistant in such a series of cases in 1946, 38% in 1947, and 59% in 1948. She also showed that in the hospitals concerned a high percentage of the nursing staff carry penicillin-resistant strains of *Staph. pyogenes* in the nose—the probable source of the trouble. My own recent experience is entirely corroborative. In hospital we have to treat increasing numbers of staff and patients suffering from penicillin-resistant staphylococcal infections, some of them exceedingly dangerous.

The best substitute for penicillin in such cases is generally understood to be aureomycin.[1] This view appears to be based mainly on work done in the United States.[2] P. H. Long and his colleagues [3] published tables showing the first choice of antibiotics for staphylococcal infections to be aureomycin, the second choice penicillin, and the third choice terramycin; and they stated that streptomycin and chloramphenicol were of little or no value. On this basis, until recently I used aureomycin in penicillin-resistant staphylococcal cases. The results were excellent except for the side-effects—nausea and diarrhœa—which proved so objectionable in some female patients that the treatment had to be stopped about the third day. This experience led me to try chloramphenicol, and since then I have found no need for any other drug. I have not yet met with a case of *pure* staphylococcal infection which has failed to respond rapidly to chloramphenicol. Further, I am authorised to say that in the Southern Group Laboratory no strain of *Staph. pyogenes*, whether sensitive or resistant to penicillin, has yet been found to be resistant to chloramphenicol by the usual laboratory test. At that laboratory it has been found that with cultures of standard *penicillin-sensitive Oxford* staphylococcus the zones of inhibition by penicillin, aureomycin, and chloramphenicol respectively are almost identical. Practically identical zones of inhibition by aureomycin and chloramphenicol continue to be obtained in all recent strains of *Staph. pyogenes* examined at this hospital, whether these are penicillin-sensitive or penicillin-resistant.

The importance of this finding, in this district at least and at the present time, is that the drug of choice in penicillin-resistant staphylococcal infections is not aureomycin but chloramphenicol, since the latter is effective, is available, is cheaper, and causes less nausea and diarrhœa than aureomycin. How long this relatively happy position is likely to last I cannot predict. In the United States, where aureomycin and terramycin have been very freely used in the last two years or so, strains of staphylococcus resistant to these drugs are being increasingly reported. That position does not seem to have been reached in this country with any of the oral antibiotics, and while the going is good chloramphenicol would appear to be the drug of choice in staphylococcal infections as soon as penicillin-resistance is suspected or proved.

Park Hospital, London, S.E.13. **H. STANLEY BANKS.**

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1. Barber, M. *In* Modern Practice in Infectious Fevers. Ed. H. S. Banks. London, 1951.
2. Nichols, D. R., Needham, G. M. *Proc. Mayo Clin.* 1949, 24, 309.
3. Long, P. H., Bliss, E. A., Schœnbach, E. B., Chandler, C. A., Bryer, M. S. *Lancet*, 1950, i, 1139.

TENSION PNEUMOTHORAX FOLLOWING TRACHEOTOMY

SIR,—Mr. Dark's article in your issue of Feb. rightly draws attention to this important conditi I have observed 5 cases of mediastinal emphyse following tracheotomy, in 2 of which there was unilat pneumothorax.

I was disappointed that Mr. Dark gave no advi on how to prevent mediastinal emphysema and pneum thorax after tracheotomy, although this problem h been solved in masterly fashion by Forbes et al.[1] The workers found that of 120 tracheotomised patien mediastinal emphysema occurred in 41% and pneum thorax in 15%.

Prevention depends on the technique of the trache tomy operation. The cause of the mediasti emphysema is the abnormally low intrapleural tensi owing to the severe laryngeal obstruction which nec sitates tracheotomy, and the air is sucked into the tiss planes from the outside air before the trachea is opene This is the essential fact of the condition.

The steps in prevention are as follows:

1. A bronchoscope or intratracheal tube is introduc *before* the tracheotomy operation, so as to bring the intr pleural pressure nearer to normal and to ensure an adequa airway during tracheotomy.
2. The tissue and fascial planes around the trachea mu be disturbed as little as possible, so as to minimise openi of spaces into which air may be sucked; in particular, t pretracheal fascia must not be lifted away from the trachea
3. Once the pretracheal fascia is incised the rest of t operation must be completed speedily, so as to reduce to minimum the time in which air may be sucked into t mediastinum.
4. The neck incision must not be made too low, especi in children and in patients with a short neck, so as not open the upper mediastinum during the operation; but course the first tracheal cartilage must not be damaged
5. After the operation obstruction of the airway m be avoided.

Liverpool Ear, Nose, and
Throat Infirmary. **FRANCIS BAUER**

MERCURY AND PINK DISEASE

SIR,—Although Dr. Holzel and Dr. James (March are circumspect in the deductions they draw from th study of infantile acrodynia, I do not think they justified in concluding that their information "stron points to mercury as an important ætiological factor pink disease." On the contrary, *their* evidence poi the opposite way.

Apparently 37% of Warwickshire children are giv mercury, but only 7% of children in Manchester. mercury poisoning is an important cause of acrodyn more Warwickshire children than Manchester child should suffer from acrodynia, but Dr. Holzel and D James estimate the incidence in Manchester to be ab 4 times greater.

Excretion of mercury can probably be taken as evide of ingestion. Mercurial powders had been given to out of 100 Kentish children attending welfare centr yet none of these children had acrodynia.[2] Dr. Hol and Dr. James do not state whether any of the child in their much larger samples, whose mothers had u mercury, suffered from acrodynia. This is a pity, an suggest that they should make the inquiry, since mother whose child has had acrodynia will be unawa of it.

On the other hand, the early symptoms of acrody are of just the kind for which "teething powders" given; and this makes the report that half of t Manchester children with acrodynia had been given m cury of somewhat dubious value as evidence of a cau

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1. Forbes, G. B., Salmon, G. W., Herweg, J. C. *J. Pediat.* 1 31, 172.
2. Leys, D. *Lancet*, 1949, ii, 1053.

lationship. True, the mercury was stated to have been ven mostly before the onset of the illness, but this as a retrospective inquiry and the illness is not marked l by an abrupt onset. The same considerations must pply in giving value to the evidence on excretion of ercury. In the years before penicillin was produced, ercury was almost invariably given to babies with ongenital syphilis, yet nobody observed acrodynia as complication of the disease or its treatment.

The finding of high cholesterol values in 3 children ith symptoms of acrodynia, who had been given ercury, is interesting. Dr. Holzel and Dr. James do ot state whether they found such values in other cases, nd I know of no observations on this point; but it hould be well worth while to find out if a high blood-holesterol is common either in acrodynia or after ngestion of mercury.

I should like to congratulate these workers on their ttempt to clear up this question of the possible signiicance of mercury in acrodynia, and I hope that with the arge number of cases to which they have access they ill continue it. My criticism may perhaps be taken in he light of Dr. Colin White's stimulating article (in he same issue), in which he says: "Those who attack theory are most likely to find its weaknesses; and if it s well founded, this fact can be revealed more convincingly by the failure of critics than by the endorsement f friends."

Children's Department,
Farnborough Hospital, Kent.
DUNCAN LEYS.

AN UNUSUAL EPIDEMIC

SIR,—In your annotation of Feb. 9 you mention a minor epidemic of "acute labyrinthitis" in which the main symptom was severe vertigo. In your opinion "it seems very possible that these are cases of a virus infection."

I saw similar cases in the form of a minor epidemic in 1925 and of a larger one in 1934.[1] The main symptoms were very severe vertigo accompanied by nausea or vomiting. In some cases hypotension and hypothermia were present. Clinical and laboratory examinations were negative. In all cases recovery was complete, though in some mild symptoms persisted for a time. Small doses of quinine and bromide seemed to have a beneficial effect.

I expressed the opinion that the disorder might be due to involvement by a neurotropic virus of the vestibular nerve or its nucleus.

University of Salonica,
Greece.
C. ALEXANDRIDES.

INTRATHECAL AUREOMYCIN IN MENINGITIS

SIR,—Where is the infection in purulent meningitis? Is it in the subarachnoid space, or on the surface of the brain and cord in the vascular pia mater? If, as I understand it, it is in the latter place, what is the point of treating meningeal infections by intrathecal antibiotics? We know that they cannot pass through the pia.

Are not Dr. Ainley-Walker and Dr. Bosanquet (March 1) guilty of a serious disregard of first principles? They support their advocacy of the intrathecal route by citing four cases of meningitis treated by local injections of aureomycin—in three cases into the subarachnoid space, and in a fourth case into an abscess (presumably after aspiration). It is noteworthy that the fourth patient was the only survivor and the only one to be given aureomycin by the systemic route. Of the three fatalities, two were caused by secondarily infecting organisms which must have been introduced at same stage by the lumbar puncture needle. What if the cerebrospinal fluid did become sterile on culture ("although intracellular cocci were still seen in the films" in one case)? Is not this to be expected if a more than adequate concentration of the inhibiting antibiotic is present in the cultured fluid?

The treatment of tetanus by the intrathecal route has long been abandoned. It is time that we ceased to put remedies into the inflammatory exudate in meningitis, and concentrated instead on efforts to get them to the causative organism through the blood-stream.

County Hospital,
Whiston, near Prescot.
J. A. MARTINEZ.

MEDICINE WITHIN THE ATLANTIC COMMUNITY

SIR,—I have read Dr. Meiklejohn's recent papers about the United States with great interest. In the second of these (Feb. 16) he mentioned the Horse Shoe Club. As hon. secretary of this club I feel that this is an opportune moment to give some further details of what the club is attempting to achieve. This can, I think, be most concisely conveyed under a number of headings:

(*A*) *Help to American Medical Workers*

1. On short visits. Those coming to Great Britain for a few days or weeks are usually more senior members of the profession. They may be coming at the invitation of the Ciba Foundation or under the auspices of W.H.O. and other organisations. Detailed plans have usually been made for their entertainment. In addition Dr. H. A. Sandiford, of the International Medical Visitors' Bureau at B.M.A. House, has an excellent organisation to help this type of visitor. The Horse Shoe Club can help any in this group who wish to visit particular hospitals or to contact British colleagues in their own specialty. There is also a fund available to members of the club to help to entertain these visitors.

2. On a long stay of 6–12 months. Those American doctors who are in Great Britain for long periods supported by a fellowship grant are usually younger, and may have few contacts in this country. The club is anxious to hear of this group so that it may offer them any help in making such contacts, and in entertaining them when the opportunity arises.

3. The medical services of the United States Armed Forces. The club is at present organising a scheme by which medical officers in the United States Air Force who are given one week's study leave have an opportunity of meeting consultants in their specialty and of visiting British hospitals. If this scheme is a success it is hoped that it will be extended to the other services.

4. Proposed visits or exchanges. The club receives inquiries from the United States and tries to put the American doctor in touch with the relevant individual or organisation in Great Britain who may be able to give help.

(*B*) *Help to British Medical Workers*

The club feels that it can contribute most by attempting to help those of senior registrar status who wish to visit the United States as part of their training before obtaining a consultant post. It is realised that a limited number of research fellowships are granted by the Rockefeller Foundation, the Nuffield Foundation, the British Postgraduate Medical Federation, the Commonwealth Fund, and other organisations. There are also several excellent schemes of exchanges between individual hospitals. It must be recognised, however, that fellowships from a dollar source are very often arranged by personal contacts across the Atlantic. It is by this method that the club may be of assistance. We are in the process of forming an American section of the club, so that we may have more opportunity of making contacts at a large number of American medical centres. We hope that we may hear of any senior registrars who wish to visit the United States (perhaps through the registrars' group of the B.M.A.); we will then do our best to help them. It should be made clear that the Horse Shoe Club acts as a kind of medical domestic agency and has no funds available for granting fellowships.

The problem of direct exchanges of doctors is more difficult. Success would depend on an agreed mechanism by which each would receive the equivalent of the other's salary, and the position is further complicated by the present exchange regulations. The club has been investigating ways of overcoming these difficulties.

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[1] Alexandrides, C. *Hellen. iatr.* 1937, no. 4.

As a matter of interest it is estimated that a senior registrar who is married can manage in the United States on a fellowship of $3500 per annum, taking his wife and one or even two small children with him.

The club is at present a small organisation with about 80 British members (not all doctors). It is hoped that those who have visited the United States and can help in establishing contacts will get in touch with us and may be interested in joining the club.

St. Bartholomew's Hospital,
London, E.C.1.

C. S. Nicol.

CANICOLA FEVER

Sir,—In connection with your leading article on canicola fever,[1] I should like to recount my experience of leptospirosis bovis treated by penicillin.

In 1949 a plague of mice in the coastal zone of this country led to an epidemic of leptospirosis bovis. Up to that time this disease had been thought to be confined to workers in contact with cattle, dead or alive. Dr. Van der Hutten, director of the Israeli Government Veterinary Laboratory, informed me that the rodent plague was undoubtedly to blame, because field-mice (*Microtus guentheri*) had been proved to be carriers.

In a village of 300 adults, all agricultural workers, 47 were affected—approximately 15% of the adult population. This was during the period May–November, 1949. A blood test for leptospirosis was carried out in 32 cases, and in 25 cases it was positive for *Leptospira bovis* or *L. grippo-typhosa*. There is thought to be no difference between these two types of leptospira.

As physician of this village I was able to give penicillin some hours after the appearance of the first symptoms (high temperature, intense headache, stiffness of the neck, blood and albumin in the urine). At this time I was giving penicillin in beeswax, 300,000 units twice daily. When the temperature had returned to normal after 24–48 hours, the dosage was reduced to 300,000 units once daily for three or four days. Of 36 cases treated in this way all reacted favourably; but *in 9 iridocyclitis occurred during the following six months.*

In your leading article you mention that penicillin treatment has effected a dramatic improvement in dogs, although it was proved that these were carriers up to 4½ years later. In my experience penicillin also causes a dramatic improvement in man; but man also remains a carrier, as is evident from the complication of iridocyclitis which developed up to six months *after* apparent cure. Nevertheless penicillin was comparatively effective, as the following observations show:

1. In most cases the temperature rose after the first dose of penicillin. One patient had a temperature of 108°F four hours after the injection. This was a typical Herxheimer reaction.
2. In 3 cases when the temperature had returned to normal I was compelled (owing to shortage of penicillin) to discontinue the treatment; and after three days the temperature rose.
3. In none of the cases treated with penicillin was jaundice noticed. Of 11 minor cases, not treated with penicillin, 5 had obvious jaundice.
4. *2 patients who were admitted to hospital for social reasons and did not receive penicillin had a high temperature for some weeks.* All patients treated by me with penicillin experienced a drop in temperature after 24–48 hours.
5. At the end of the epidemic—and owing to the noticeable success of penicillin treatment—the population of the village informed me immediately of any suspected fresh cases; so I was able to commence treatment at once. The agglutination reaction in these cases was negative.
6. In other areas of the coastal zone where penicillin treatment was not given the cases were more severe, and a large number of patients were sent to hospital. In the hospitals penicillin treatment was not so effective, owing, in my opinion, to the delay of 4–6 days between the onset of symptoms and the start of treatment.

Rishpon, near Herzlya,
Israel.

Werner Cohn.

BARBITURATES ON THE BRAIN

Sir,—I read with interest your annotation of Feb. It would be interesting to know whether barbiturates a blessing or a curse so far as the general practiti concerned. Hospital physicians are prone to deal these drugs—usually the more expensive brands—with a somewhat lavish hand, and they gi no indication of how long administration is to be co tinued. The barbiturate habit is easy to acquire, a the phenobarbitone habitué can soon become to h doctor the phenobarbitone bore. Barbiturates depr many people and make them peevish and sometim hateful to their families. Let anyone who doubts th take a few doses of phenobarbitone.

To many of my patients gr. $^1/_3$ phenobarbitone table are merely " those little things like saccharin," and som times it would be as well if they retained this aura innocence.

A young man, warned that they should be put out of t way of children, two nights later, merely to spite his wi swallowed thirty of them at once and thereby took an ea flight into notoriety, which he probably would not have do had their potential danger not been pointed out to him.

An old lady whom I had been trying to wean off her phen barbitone said rudely: " Give us some of them phen *barbitone tablets—a lot. My sister's doctor gives* her plent and she sends me some."

It is easy to hand out such prescriptions, but is it fa to the patient (assuming that he is not epileptic) encourage *him to be always facing the ordinary* difficu ties of life in a kind of barbiturate haze? Even the ru old lady now admits that the tablets do not do her a good. Much will depend on the persistence of the patie *on the one hand and on the* " *sales resistance* " of t doctor on the other.

Bertrand Russell says: " In the modern world t excess of fear above the level which may be called ration *is more marked than ever before,* because the habit fear persists while the occasions for fear have great diminished." The subconscious fears of the recent pa and the realisation that life in a world hag-ridden wars and rumours of war is, more than ever, " nast brutish, and short " will no doubt make us decide continue prescribing barbiturates; but let us do it wi some circumspection, especially when we are in t position to give the first dose.

G. L. Davies.

Brighton.

TOXIC EFFECTS OF DIAMINODIPHENYLSULPHONE

Sir,—We should like to comment on the article Dr. Allday and Dr. Barnes. which appeared in your iss of Aug. 4. During the last three years we have treat over 3000 cases of leprosy with diaminodiphenylsulpho (D.A.D.P.S.) and cannot *agree that it is too toxic.*

To take the points as they arise in the article:

Dosage.—We have found that this need not exceed 0·4 weekly. Excellent results are obtained with this dosag which may *be safely* continued for months and if necess years with *only* short rest periods.

Toxic effects.—There are people who are sensitive to su phones, just as there are people sensitive to sulphonamid or aspirin or eggs; and if given sulphones these people w produce the syndrome described (dermatitis, jaundice, &c. In our original groups—some 350 strong, including India Malays, and Chinese—we had no single case of this, b when we increased our numbers to about 1800 4 cases d occur, 2 ending fatally with acute yellow atrophy. T danger-signal of dermatitis was not recognised as such, a both received further doses of sulphone after the onset the dermatitis. Since then, we are glad to say, there h been no fatalities in two years, though occasionally dermati *has occurred* in new cases in the period of the 8th–1 dose—i.e., 2nd–3rd month. The risk of fatalities see to be vastly reduced by recognising this danger-signal a immediately withholding sulphone.

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[1] *Lancet*, 1951, ii, 1169.

eactions occur, but with the progress of treatment become severe and less frequent. Psychosis is encountered, we sider, only in those with a previous history of mental rder. Neuritis, headache, and anæmia are all minor urbances which are usually easily corrected.

n conclusion, we maintain that for safety, efficiency, cheapness D.A.D.P.S. at the moment is the sulphone choice, and injection in oily suspension is the safest te. We would add a warning about changing sulphone-sitive cases to thiosemicarbazone: from this, too, we ve seen death from subacute yellow atrophy.

ungei Buloh Settlement,
Federation of Malaya.

B. D. MOLESWORTH
P. S. NARAYANASWAMI.

THE TREATMENT OF PEPTIC ULCER

SIR,—In his usual trenchant style Dr. Jennings has de three main criticisms of our recent paper; one these is of considerable general interest. According to . Jennings no therapeutic trial "in which we treat e patient and attempt to increase his resistance . . . has y practical value unless it tests the possibility that ferent individuals react differently." This would seem be a truism, but from the context it appears that . Jennings believes that it makes invalid a customary rm of clinical trial that has been developed by the edical Research Council's Statistical Research Unit. fact the trial tests whether similarly selected groups individuals treated in different ways respond, in terms group phenomena, in the same way. The value of a oup trial cannot be questioned because the treatment nployed helps some of the patients in the group and ot others. An over-all difference will be shown unless, rarely happens, the treatment affects the same number patients in the group in exactly opposite ways. Even is result can be checked by seeing whether the group as a disproportionate number of very good and very ad results within it. Few research-workers—least of all atisticians—now rely on averages alone. In the trial f phenobarbitone in our patients there were fewer xtremes of response in the treated series than in the ntreated; so it is unlikely that the lack of effect of henobarbitone can be attributed to counter-balancing f effect within the group. It was, in any case, the outine use of phenobarbitone that was under trial; r many practitioners prescribe it as a matter of course n the treatment of gastric ulcer. Incidentally, Dr. ennings is wrong in thinking that the M.R.C. Statistical Research Unit's method of group trial contravenes Prof. R. A. Fisher's teachings. It would indeed be trange if it did, considering the esteem in which his eachings are held by the whole unit.

The second criticism appears to be based on the surprising contention that the size of the ulcer crater and of the niche are unrelated to one another. In our view, the area of the niche, when the radiographic projection obtained is tangential to the general outline of the inner surface of the stomach in the region of the ulcer, gives the only practicable measurement of the size of the ulcer that can be repeated in the living subject. We are aware that the shape and size of the ulcer in the excised specimen is not identical with that of the radiographic niche, but both are aspects of the same ulcer viewed in different circumstances. The general reliability of the yardstick adopted for the measurement of the size of the crater was confirmed in our series by the experience gained in gastroscoping each patient the day after the initial radiographic examination. The pseudodiverticula to which Dr. Jennings refers are generally nconstant in appearance, and, though they may create difficulties in interpretation at isolated examinations, they rarely cause confusion subsequently.

The third criticism evidently derives from a misunderstanding. No claim was made that the patients in the trial were representative of all gastric ulcer patients and no conclusion was drawn about the specific value of any form of diet. It was, in fact, clearly stated that it was not known whether the better response of one group of patients "was due to the rest in bed or to the diet"; the practical conclusion that patients should be kept in hospital until healing was complete was limited to "those gastric ulcer patients whose condition merits admission," and was moreover qualified by the proviso that this was advised only if it was believed that the patient's prognosis could be improved by securing healing of the ulcer.

Dr. Jennings says that "there is a reason for most gastric ulcers and if you get rid of the cause the ulcer will heal." May it prove to be so simple. We ourselves do not know the causes of gastric ulcer; and if, as it appears, they are known to Dr. Jennings, we would beg him to publish an account of them. Meanwhile we shall continue to undertake trials of various remedies (old and new) in the search for some relief for the patient. We do not propose, however, to run inter-hospital competitions as part of our trials. It would appear more worth while to try methods more generally applicable than sending patients on the rounds of the hospitals.

Central Middlesex Hospital,
London, N.W.10.

RICHARD DOLL
FRANK PYGOTT.

SIR,—Mr. J. E. Richardson evokes the Red Queen; but the traditional red herring would have been more appropriate, for his letter is at once misleading and tangential to the main body of the recent correspondence on peptic ulcer. He takes me to task for instancing the starvation treatment of hæmatemesis patients as "an old and traditional" method and points out that feeding of these patients was in fact introduced, not recently, but in the early years of this century by Lenhartz. It is true that Lenhartz revolted against the *complete* starvation of ulcer patients, and with great daring allowed very small feeds of milk and egg. The slightly modified, but no more liberal, Lenhartz diet in use in this country allowed two-hourly feeds of milk or milk and egg of 1 oz., $1^1/_2$ oz., 2 oz., $2^1/_2$ oz., and 3 oz. on the first five days respectively. If the patient had a relapse, he was returned to the bottom of the scale, as in Snakes and Ladders, at a time when he was most in need of sustenance. As a cause of dehydration and iatrogenic death it was quite unsurpassed in middle-aged and elderly patients with bleeding chronic peptic ulcers. I have previously reported in detail the effects of this therapy in producing death with profound extrarenal uræmia.[1]

Mr. Richardson and his colleagues are fully entitled to regard this as feeding, but I regard a diet which does not provide basic calorie requirements before the tenth day as a starvation régime. Feeding of hæmatemesis patients in the accepted meaning of the term began with Meulengracht in the middle 1930s.

> "When *I* use a word," Humpty Dumpty said in rather a scornful tone, "it means just what I choose it to mean, neither more nor less."
>
> "The question is," said Alice, "whether you *can* make words mean different things."

Department of Gastro-enterology,
Central Middlesex Hospital,
London, N.W.10.

F. AVERY JONES.

SIR,—The subject of the treatment of peptic ulcer seems to have been little clarified by Dr. Todd's paper (Jan. 19), which Mr. Tanner (Feb. 2) thought was based on flimsy arguments, or by the paper of Dr. Doll and Dr. Pygott (Jan. 26), which Dr. Jennings treats rather roughly in his letter on March 1.

Dr. Jennings mentions nine "unstated" points which necessarily vitiate Dr. Doll's conclusions, but he does not apply a very rigid discipline to his own reasoning.

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[1] *Brit. med. J.* 1939, ii, 332.

I was interested to note that Dr. Jennings does not prescribe a milk diet for his peptic ulcer patients but keeps them on a normal diet. Would he care to define a little more precisely what he means here by "normal"? It might then be found that the psychiatric element in his method of treatment was somewhat superfluous.

In his article last week Dr. Lawrence reports better results from a "normal convalescent diet" than from a modified Lenhartz régime. He emphasises that "those on full diet had the ordinary hospital meals (including fried foods, cheese, and pork pies)" supplemented by milk twice or thrice daily. It would be helpful to know whether the "controls" were made to eat all they were given, or whether they were allowed to choose foods from a menu which they found by experience suited them best.

London, W.1. J.-JACQUES SPIRA.

HICCUP DURING ANÆSTHESIA

SIR,—The method suggested by Dr. Fajardo (Feb. 2) in order to eliminate hiccup during anæsthesia—injection of 20 mg. of 'Methedrine'—takes 3 minutes and is followed by hypertension. The inhalation of the vapour from an ampoule of amyl nitrite, suggested by Dr. Lee (Feb. 16), acts in 30 seconds but is accompanied by hypotension.

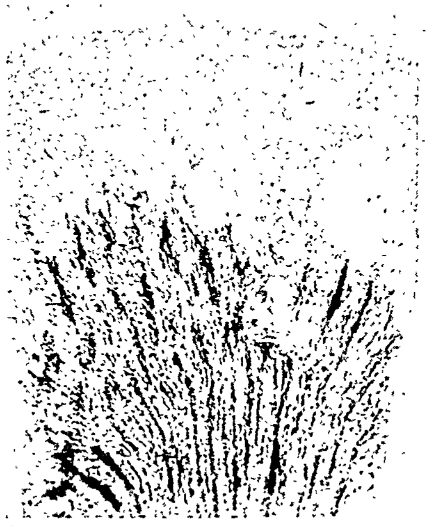
Perhaps a simple procedure which I have discovered by chance, and which is effective in less than 5 seconds, might be useful to some anæsthetists. Simply take a rubber catheter 4–6 mm. in diameter. Introduce it into the patient's nostril until it reaches the pharynx and tickles the posterior wall. It will irritate a reflexogenic zone and immediately stop the hiccup.

University Clinic of Gynæcology
and Obstetrics, Geneva. I. BONSTEIN.

SHUNTING IN THE HUMAN KIDNEY

SIR,—It was interesting to read the article by Professor De and Dr. Sengupta in your issue of Dec. 15. They demonstrate ischæmia of the renal cortex with the help of Pickworth's stain and state: "no clearer demonstration has been reported of the shunt in the human kidneys, so far as we can gather."

The so-called Pickworth's stain is a well-known method of demonstrating ischæmia. The method is more often known among histologists, after its originator,[1] as the Lepehne reaction or benzidine reaction.[2] We believe that with the help of this method one of us was first successful in the direct anatomical demonstration of the Trueta phenomenon in human pathology (see figure).[2] Since then we have several times found similar changes in kidneys, especially in cases of great water-loss, eclampsia, and surgical shock.



Section of kidney showing benzidine reaction: glomeruli and intertubular capillary network of renal cortex completely ischæmic; and vasa recta, deriving from efferent vessels of juxtamedullary glomeruli, highly hyperæmic. (Reproduced from paper by Solymoss.[2])

Such observations suggest that the intrarenal bl distribution first detected by Trueta et al. in brilliant experiments plays an important part in clinical conditions.

Department of Pathology,
Municipal Hospital,
Szombathely, Hungary.

B. SOLYMOSS
J. MOLNAR.

PSYCHOLOGY AND THE MATERNITY UNIT

SIR,—Dr. Tylden's article (Feb. 2) and subsequ comments by various correspondents illustrate the pa dox that while psychological factors are now general believed to contribute toward difficulty in labour, t extent of their influence and its obstetrical significan have not been satisfactorily determined. Psychiat investigation of patients who have had difficult lab often reveals long-standing emotional conflict, but it probably unsound to assume a causal relationship every case. Unmarried mothers, who of all women mig be expected to be anxious and unhappy, do not see to have significantly more difficulty in labour than th more fortunate sisters.

It would be of the greatest value to obstetricians foreknowledge of the patient's state of mind could used to predict uterine dysfunction; and even more this complication could be prevented by timely treatme of the causative factor. Any inquiry during pregnan into personality factors or emotional conflicts which ma possibly be related to future obstetrical difficulties complicated by the fact that adequate psychologic investigation must always be to some extent therapeut and may possibly modify the patient's psychologic state before she meets the test of labour. Present obje tive psychological tests of personality factors may n prove especially reliable in this particular type of proble and psychologists may have to be content with mo subjective methods of assessment until further tests a developed. It is important that any experimental seri be compared with controls, and that in both grou account should be taken of such matters as age, pari and physique, which all have important effects upon t efficiency of labour.

It would be instructive to compare the actual perfor ance in labour of a group of women who have undergo full antenatal training in "natural childbirth" and o group who have not. Interpretation of the behavio and emotional attitudes of women in labour has prov most difficult in our experience, since there seems lit constant association between such subjectively estimat criteria as apparent emotional or physical tensio coöperation, and efficiency of effort in the second sta and type and degree of emotional response toward t baby after it is born. *Efficiency* of labour should pref ably be judged by objective and measurable standar such as the duration of labour, the episiotomy, force delivery, and cæsarean-section rates, the incidence fœtal distress and stillbirths, and subsequent success lactation.

Investigations under way in this unit, while not y conclusive, tend to confirm that nervous and ill-adjust women as a group are more prone to uterine dysfuncti during labour than are more emotionally stable patient The traditional unpredictability of womankind, howeve has so far obscured any clear correlation between speci and definable psychological traits and clearly recognisa characteristics of labour.

Those who strongly advocate home confinement f psychological reasons appear to be basing their argume on insufficient evidence. The tendency seems to be contrast the best of homes with the worst of hospita whereas the choice before the patient is often the oppos Fear of hospitals is largely a matter of social custo In Canadian cities delivery in hospital is almost univer

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1. Lepehne, G. *Beitr. path. Anat.* 1919, 65, 183.
2. Solymoss, B. *Lancet*, 1949, i, 957.

Winnipeg less than 2% of all births now take place ome), and most Canadian city-dwellers would now ome highly anxious at the idea of having a baby where but in the "safety" of a modern hospital. same trend is obviously developing in British centres re adequate facilities are available. It does not seem ly that any psychological advantages which may be med for domiciliary midwifery will continue to pensate for its many obstetrical disadvantages.

berdeen Maternity Hospital. D. B. Stewart.

ir,—Dr. Tylden states that the physiotherapist has ore correct approach to natural childbirth than some lwives. Physiotherapists have learned this approach n the pioneers of antenatal training for mothers, all whom are either obstetricians or midwives. Miss nie Randell, herself a midwife and physiotherapist, t introduced this branch of physiotherapy, which has e developed and is now practised all over the country. Vithout the full coöperation of the obstetrical team re is a danger of producing confusion in the mind the mother. Happily this is the exception rather n the rule, and the physiotherapist feels that she has ceeded when a "trained" mother is able to put o practice all that she has learned in the antenatal sses, so that in labour she is confident, independent, l coöperative. Under these circumstances there is no d for the physiotherapist to take any part in the ond stage of labour.

ondon. Mary Phillips.

Sir,—Most of your correspondents seem to agree the desirability of training women for childbirth. a lay woman I feel that there are three outstanding cessities: (1) to teach complete relaxation; (2) to e instruction on the character and mechanism of our, with all questions answered; and (3) to ensure far as possible—particularly in midwives, who are th the patient early in her labour—a full understanding the influence of the emotions on normal childbirth. some hospitals mothers are given these opportunities d may enjoy happy childbirth. But in others one s only to mention natural childbirth to call forth marks about "cranks."

I noticed that Dr. Tylden mentioned the women's agazines. I have been pleasantly surprised at the good lvice and clear explanation of the psychology of childrth often given in these. It seems very sad that many omen, getting such an introduction to the possibilities natural childbirth, will have their hopes dashed by arrow-minded and out-of-date members of the medical rofession.

York. Gwendoline Rowntree.

BOVINE TUBERCULOSIS PREVENTS HUMAN TUBERCULOSIS?

Sir,—As far as Jersey is concerned Mr. Pitcher's tter (Jan. 26) gives a wrong impression of the facts. uberculosis mortality has fallen steadily in Jersey, as England and Wales, since the beginning of the century. t has usually been at a slightly higher level than in ngland and Wales, but the fall has been parallel.

Bovine tuberculosis, as far as is known, has never een widespread in the Jersey herd. It was not eliminated y a campaign of testing and slaughter; it was never here. Tuberculin testing was introduced simply to atisfy the market, a large proportion of which is in the .S.A. No cattle can be exported unless they are uberculin-negative.

As to human tuberculosis, little or no special proision was made in 1925, and the few admissions in that ear are no indication of the amount of the disease. The umber of deaths from all forms of tuberculosis in 925 was 49, giving a mortality-rate of 98 per 100,000. he number of deaths in 1946, before the introduction of streptomycin, was 27, giving a mortality-rate of 54 per 100,000.

Jersey has a population of approximately 57,000, and there are apt to be considerable chance variations in the rate, so it is better to take the average mortality for five years. The average number of deaths in 1924–28 was 53·8 per annum, and the rate 107·6 per 100,000. The average number of deaths in 1944–48, which included sixteen months of the occupation, was 40, and the rate 86·2.

Nowadays much greater provision is made for the treatment of pulmonary tuberculosis, and an active case-finding campaign is in existence; so quite naturally the number of admissions has increased. The death-rate from all forms of tuberculosis in 1950 was 33 per 100,000.

The introduction of bovine tuberculosis into the island would be a disaster to one of our main industries, and would lead to the death and maiming of many of our children even if it reduced the mortality from adult tuberculosis. B.C.G. is a better answer, and we are carrying out an extensive B.C.G. campaign.

Jersey,
Channel Islands. R. N. McKinstry.

PLASMA SUBSTITUTES

Sir,—I read with interest the reports[1] on 'Plasmosan' by Dr. Thrower and Dr. Campbell, and by Dr. Arden and his colleagues. In the same number you summarised in an annotation the plasma substitutes as follows: gelatin, dextran, and polyvinylpyrrolidone.

I know that these are good plasma substitutes; but rationally the best, by its more physiological nature, is desanaphylactised animal plasma (D.A.P.), made by Massons's original method. Experimentally and clinically, D.A.P. has been used very successfully in every condition which requires a plasma—or sometimes a blood—transfusion. Massons described his method in your columns[2]; and his article was commented on in an annotation in the same issue. Since that report appeared experience has shown how right Massons was in his description and conclusions. Scientifically a large number of reports, and commercially 'Isoplasma' in Spain and 'Heteroplasma' in Portugal, testify to the validity of his findings.

University of Barcelona. J. García-Llauradó.

ECONOMY IN HOSPITALS

Sir,—Your leading article of March 1 makes some excellent suggestions, but in general the effect of notices and exhortations is disappointing and the growth of a sense of responsibility in the minds of consultants is likely to be too slow to help much in the present emergency. I feel much more optimistic about the results of administrative changes and I should like to make some additions to those which you propose:

1. Set out a new definition of the duties and responsibilities of regional hospital boards and hospital management committees, so that with a clear conception of respective functions overlapping and duplication of services may be avoided.
2. Allot money to each management committee to some extent according to the population of the catchment area and the proportion of the work of the region which is undertaken, instead of basing the amount on the expenditure in previous years.
3. Set out a special budget for medical education to provide for the higher standard of expenditure in teaching hospitals, instead of allowing this to be a charge on general health service funds.
4. Review all planning made in the regions since the appointed day, giving special consideration to such things as size of management committee groups and the setting up of groups for certain diseases, such as tuberculosis and cancer.

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1. Thrower, W. R., Campbell, H. *Lancet*, 1951, i, 1096. Arden, G. P., Mandow, G. A., Stoneham, F. J. R. *Ibid*, p. 1099.
2. Massons, J. M. *Ibid*, 1946, ii, 341.

instead of fitting these conditions into the general hospital service.

5. Rationalise medical staffing in the way you suggest and also in the arrangements for working in hospitals. Duties should be properly distributed in the consultant, assistant consultant, registrar, house-officer hierarchy. Alter the terms and conditions, which are now financially better for those undertaking 9 sessions than for those working whole-time. Stop the irrational system of advertising posts as maximum sessions or whole-time at the option of the successful candidate.

6. In all administrative arrangements treat doctors as ordinary members of the community—perhaps a little more honest than business men and lawyers, and a little less honest than civil servants!

Walton Hospital, Liverpool. HENRY H. MACWILLIAM.

POTENTIAL DANGER IN ENDOTRACHEAL INTUBATION

SIR,—Some of the newer armoured endotracheal tubes are made by investing the wire spiral in 'Latex' rubber.

My attention was drawn by my theatre orderly, Mr. Parfitt, to bubbles within the wall of the tube after sterilisation by boiling. In some instances I have found that the bubble is inside the lumen of the tube, leading to its partial or complete occlusion. Since the bubble is pneumatic there is no interference with the passage of a stilette down the tube, but there is undoubtedly a danger of occult respiratory obstruction. I have removed these bubbles by aspiration with a hypodermic needle while looking down the endotracheal tube held to the light.

It would seem desirable to sterilise these tubes by some method other than heat.

Plastic Surgery, Burns, and Jaw
Injury Centre,
St. Lawrence Hospital,
Chepstow, Mon.

HARRY MIDDLETON
Anæsthetist.

ANÆMIA IN AFRICANS

SIR,—Dr. Hutton's (Jan. 12) cases of anæmia at Mulago seem to be very similar to those we have found in Malaya among the Southern Indian estate labour population. In these people, with moderate hookworm infestation, who are on a low-protein diet, we found it possible, by means of oral iron, bed rest, and hospital diet, to raise the mean Hb level from below 4 g. per 100 ml. to about 9 g. per 100 ml. at which point it remained stationary. At this level in half the cases macrocytosis was observed, which was regarded as due to the reticulocyte response and was not influenced by folic acid, liver, or vitamin B_{12}.

Over a period of two years we have searched for megaloblastic macrocytic anæmias with small success. Approximately 2000 Indians, Malays, and Chinese have been screened by a preliminary hæmoglobin estimation. Of these, 180 who showed a hæmoglobin of below 6 g. per 100 ml. were investigated hæmatologically. 3 of these showed a macrocytic anæmia, which was combined with a megaloblastic marrow, and they all responded to folic acid. It would appear that the prevalence of this type of anæmia in Malaya has lessened in recent years, as Cowan [1] readily found numerous cases and one of us (J. P. F. W.) investigated and treated a series in 1948.

Institute for Medical Research,
Kuala Lumpur, Malaya.

J. P. F. WHELAN
ELIZABETH CHEEK.

SIR,—I was interested to see that Dr. Foy and Dr. Kondi (Feb. 23) refer to finding giant "stab-cells" in the marrow in a substantial proportion of cases of iron-deficiency anæmia.

In my experience it is not uncommon in iron-deficiency anæmia to find giant metamyelocytes with nuclei almost, if not quite, as complicated as those associated with pernicious anæmia; and I am inclined to attach so ætiological significance to their presence.

At a recent meeting of the section of pathology the Royal Society of Medicine [1], I mentioned this ma change, which I thought was well known since it referred to by such authorities as Rohr,[2] Bodley Scot and Wintrobe.[4] I was surprised that it did not seem to widely appreciated, and even a hæmatologist of gr experience expressed doubt as to its existence.

Since then I and my colleagues have re-examined considerable number of marrows for this feature, and even more convinced that it is fairly common. Perha the speaker who raised the point by attributing to th cells a specific diagnostic significance in relation to megaloblastic anæmias, gave the answer when suggested that few people take the trouble to investig the marrow in iron-deficiency anæmia.

Department of Pathology,
King's College Hospital,
London, S.E.5.

WILLIAM M. DAVIDSON

PROPHYLAXIS AGAINST TETANUS IN BURN

SIR,—I share Dr. McLaren's opinion [5] about frequency of tetanus as a complication of all types injury among primitive peoples in the tropics.

About 75% of the cases of tetanus that I have se in the Uele district of the Belgian Congo have be among natives who had been seriously burned. Th seems due to the custom in the Babua tribe of treati burns by local applications that include earth. In the cases tetanus was always fatal in 24–48 hours, no do because of the massive infection.

Having observed during each of the years 1941- about 10 such cases, I adopted routine prophylac injection of antitetanus serum in all cases of seri burns; and this complication no longer appears.

Tetanus after burns rarely develops in the Stanleyvi district, where tetanus is otherwise no less comm than in the Uele district, but where the native meth of treatment is not in use.

Stanleyville Hospital,
Belgian Congo.

P. LIMBOS
Medical Directo

FAMILIAL INTESTINAL POLYPOSIS

SIR,—Dr. Wolff's interesting paper (March 1) on case of familial intestinal polyposis with pigmentation lips, oral mucosa, face, and digits, prompts me to rec briefly a case which I saw some time ago at the Itali Hospital, which suggests the existence of incompl forms of this rare condition.

An Italian man, aged 72, came to the outpatient departm with moderately severe right hemi-parkinsonism. He g no history of gastro-intestinal trouble. He was found to h fine melanin pigmentation around the mouth, but not on fingers. There was conspicuous pigmentation of the o mucous membrane and the soft palate. Barium meal a barium enema showed no evidence of polyposis, but sigmoi scopy showed two polyps about 12 cm. from the anus. T appearance of these was exactly the same as that described Mr. Norman Tanner.[6] The blood-pressure was 220/105 m Hg. There was no clinical or biochemical evidence of sup renal deficiency or of hæmochromatosis, and the Wasserma reaction of the blood was negative.

The patient had three daughters, none of whom had h gastro-intestinal complaints. All three showed pigmentati of the oral mucous membranes, and one had additio pigmentation in the circumoral region.

Unfortunately, the patient's daughters refused a investigation other than a general clinical examinati and I could not see any of the patient's siblings.

E. MONTUSCHI

London, W.1.

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[1] Cowan, G. A. B. *Trans. R. Soc. trop. Med. Hyg.* 1948, 41, 525.

[1] See *Lancet*, 1951, ii, 1067.
[2] Rohr, K. Cited by Scott, R. B. (footnote 3).
[3] Scott, R. B. *Quart. J. Med.* 1939, 8, 138.
[4] Wintrobe, M. M. Clinical Hematology. London, 1951; p. 6
[5] McLaren, D. S. *Lancet*, 1951, i, 1325.
[6] *Proc. R. Soc. Med.* 1951, 44, 415.

WAYS OF USING MASS RADIOGRAPHY

SIR,—The findings of Dr. Halliday Sutherland (Jan. 19), enchard and Grenville-Mathers,[1] and others, notably ynon,[2] that a large yield of active tuberculosis cases to be found amongst patients referred by general actitioners for routine chest radiography, is not rprising considering that some 95% of all notified ses of pulmonary tuberculosis have reached registration rough the surgeries of general practitioners. What rhaps is surprising is that more mass-radiography its have not concentrated on this group. It should be membered, however, that the great majority of units e organised on a mobile basis, and cover a very nsiderable area, in which circumstances it is not racticable to provide a constant general-practitioner rvice.

The severe shortage of X-ray film, which seems likely continue, affects not only mass-radiography units, but he chest clinics and hospital services; and this adds oint to the question whether mass-radiography techiques could not be applied more economically and uitfully on a mainly static rather than a wholly mobile asis.

Under the former arrangement an efficient general-ractitioner service covering a wide area, a service for contact xamination for several clinics, and a routine preliminary hest radiography service for hospital outpatients, could be stablished. Other selected population groups could also be overed from a static centre—e.g., school-teachers, public-ealth workers, and Service intakes. The total abandonment f a mobile policy would, however, mean that the three or our active cases per thousand examinations at present being detected in general-public and factory surveys would no onger be disclosed. There is no reason, however, why mass-adiography units, particularly those operating in the cities nd large towns, could not provide both a static and a mobile ervice concurrently. A second four-valve X-ray set and ome additional staff would, of course, be necessary, and the static centre would have to be carefully sited to give maximum coverage.

The superintendent radiographer of this unit (Mr. H. T. Lawlor) has suggested that the fitting of an 'Odelca' camera to the static set would greatly reduce the need for large films, both in respect of examinees referred directly to the static centre, and of recalls arising from the mobile service. The individual 70 mm. plate could be sent with the report to the physician concerned, in the same way as large films are sent at present. The 70 mm. film can be easily scrutinised with the aid of a magnifying-glass.

The development of the mass-radiography (or miniature radiography) service on the above lines might do much to reconcile the various views on the utilisation of mass-radiography units.

Mass-radiography Unit 6B,
London E.13.

D. J. LAWLESS
Medical Director.

SIR,—The correspondence on this subject suggests to my mind the question: Why should we not use the opportunity provided by mass miniature radiography to bring together some millions of our adolescent and adult population for some form of health check-up? Recently, after volunteers of the corporation male staff were examined radiographically, facilities were offered for testing of urine in an endeavour to identify cases of unsuspected diabetes.

The opportunity might well be used for a full health examination. If this were not possible, then attention could be directed to certain examinations, such as audiometry, blood-pressure, foot defects, and blood examinations. This work need not interfere with the mass-radiography examination as it is done after the volunteers have been examined radiographically. The difficulty, of course, is to provide staff for this work, but the idea might be tried out more extensively in those areas where the necessary staff is available. My recent small experience of an endeavour to discover early cases of diabetes warrants this view; and I found that a large majority of volunteers were willing to have various tests carried out.

There are all too few measurements of health of the adult population. I suggest that we might use fully the opportunity of the mass-radiography examination to extend our knowledge of the health of men and women workers.

Experience has also been gained in this area of the value of mass miniature radiography to family doctors who send patients suffering from "chronic bronchitis" to be examined radiographically either at a special session devoted to these cases or by appointment in the ordinary way. The types of patient for whom this extension of the mass miniature radiography service is primarily intended are those in whom the symptoms of chronic bronchitis appear to be a predominant feature, and those in whom chest signs and symptoms are vague. In the differential diagnosis of such cases many local family doctors welcome an opportunity of radiographic examination. Some patients prefer to attend a mass-radiography unit rather than a chest clinic or hospital.

The linking of the family doctor with mass-radiography units in this way is not perhaps as often practised as it might be. The results here show that the incidence of active pulmonary pulmonary tuberculosis is ten times greater among "chronic bronchitics" than ordinary volunteers.

J. L. BURN
Salford.   Medical Officer of Health.

SELECTIVE RADIOGRAPHY

SIR,—Dr. Sutherland's article of Jan. 19 and the subsequent correspondence have emphasised the value in tuberculosis case-finding of selective radiography of patients referred by general practitioners. It may be of interest, therefore, to describe some results achieved in such cases by the use of diagnostic fluoroscopy.

Since May, 1949, most of the patients referred to this clinic by general practitioners for X-ray examination of the chest, as well as all adult contacts referred by health visitors, have been examined by fluoroscopy. I am indebted to my former senior registrar, Dr. C. M. Tinker, for compiling the figures given below. During 1950, 3828 patients were examined, of whom 2805 (74%) were referred by general practitioners and 1023 (26%) were contacts. The findings were as follows:

	No. per 1000
Active pulmonary tuberculosis in doctors' cases . .	33·1
Active pulmonary tuberculosis in adult contacts	5·75
Inactive tuberculosis in doctors' cases	44·8
Inactive tuberculosis in contacts	18·4
Bronchial carcinoma	7·8
Cardiac conditions	7·1
Transient pulmonary lesions (pneumonitis, &c.) . .	10·3
Miscellaneous	38·1

87% of the persons examined showed no significant lesion on fluoroscopy; and so only 200 full-size films had to be taken, saving £550 on probably normal films, and much time and labour. It will be seen that the incidence of active tuberculosis in the doctors' cases is very close to the figure of 3·4% obtained by Dr. Beynon's mass miniature radiography unit (Feb. 9). The incidence of active tuberculosis found by a mass-radiography unit in this area during a 4-month visit in 1950–51 was about 1·5 per 1000, 25 active cases being discovered during the examination of 14,500 persons. The incidence of active tuberculosis in patients from doctors' surgeries was therefore twenty times as great as in the general population.

A chest physician working with a radiographer and one nurse, and spending 4 hours weekly screening 80 doctors' cases, will detect in a year about 130 new cases of pulmonary tuberculosis, at a cost of approximately £2 5s. for each case. A mass-radiography unit examining 40,000–45,000 persons from the general population in a year will detect a similar number of new cases, but at a cost varying between £11 and £600 for each case. It will be some years before cameras taking 70 mm. or 5 × 4 in. negatives of the screen image will be generally available, and many more years before electronic enhancement[1] becomes a reality. Every chest clinic worthy of the name, however, now has an X-ray screen; and the technique of diagnostic fluoroscopy described by Hall and Tattersall[2] and amplified by myself[3] is simple, and if properly carried out will detect at least 95% of lesions visible on a full-size film, in addition to others not visible on the orthodox postero-anterior film.

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[1] Trenchard, H. J., Grenville-Mathers, R. *Tubercle*, 1952, 33, 20.
[2] Beynon, A. E. *Med. Pr.* 1949, 221, 548, 577, 602.

Let us make the best use of the means that we have while waiting for better instruments to be put in our hands. Let us also avoid duplicating effort and squandering our resources by running mass miniature radiography units in competition with chest clinics. Wherever possible mass-radiography units and chest clinics should use common buildings and common staff, and ideally every large chest clinic should have two departments, one for individual diagnosis and the other for group investigations by miniatu[illegible] arrangement which is working with [illegible] in Scandinavia.

Lancaster House Chest Clinic,
Southend-on-Sea.

E. G. SITA LUMSDEN.

ELECTROLYTE DISTURBANCES AFTER URETERIC TRANSPLANTATION

SIR,—Your leading article of March 1 draws attention to one of the complications which may follow ureteric transplantation; but it would be wrong to assume that the syndrome of hyperchloræmic acidosis is common, that the theory of chloride reabsorption as its cause is universally accepted, or that the only literature on the subject comes from America.

In 1951[4] we described the same syndrome following transplantation of the right ureter into the cæcum, and produced evidence that it was associated with damage to the distal renal tubules. This appeared to be due to increased intra-ureteral and intrapelvic pressure from a cæcum distended with urine; we found no evidence of selective chloride reabsorption in the presence of normal renal function, and considered that it played little part i[illegible] of the syndrome.

Whilst [illegible] ureters into the sigmoid colon is often followed by a slight rise in the plasma-chlorides and a lowering of the plasma-bicarbonate, we have not seen the syndrome in any serious degree except in the cases where the cæcum was used to accommodate the urine. Treatment by a retained rectal tube may prevent reabsorption of chlorides, but at the same time it diminishes the pressure in the bowel: it also defeats the object for which the operation was performed. It is noteworthy that the syndrome appears to have increased pari passu with the increasing popularity of end-to-side anastomosis whereby intestinal pressure is more readily transmitted to the ureter, as evidenced by the finding of pneumo-pyelograms in some cases.

It would be unfortunate if occasional hyperchloræmic acidosis were allowed to interfere with the logical development of an operation which is generally humanitarian and often life-saving, and we are in full agreement with the need for further research into the problem.

An investigation of the late results of uretero-colic anatomosis is being undertaken by the British Association of Urological Surgeons, and the subject will be discussed at the annual meeting this year.

Middlesex Hospital,
London, W.1.

E. W. RICHES
A. KEKWICK.

Parliament

Tuberculosis on Tyneside

IN the House of Commons on March 7, Mr. EDW SHORT pointed out that for many years the incidenc tuberculosis on Tyneside had been greater than in country as a whole. In 1919 the figure for Tyneside pretty much the same as elsewhere, but in the next years the rate for England and Wales was halved, w the rate for Tyneside dropped only slightly. Du the ten years from 1930 to 1940 the rate for England Wales increased slightly, while the rate for Newca upon Tyne and most of the Tyne area rose to alm double the national level. Since the late war there been a great improvement; but though the act position had improved, the relative position had done so. Indeed in some respects the relative posit between Tyneside and the rest of the country was wo Mr. Short himself attributed this state of affairs to rapid influx of population from rural areas and f Ireland; to a succession of slumps and depressio and to the fact that the population of Tyneside younger than in most other areas. The new tende in the North East of married women to remain in w might also have helped to increase the tubercul figures; the incidence among women between 15 and years of age had increased more than in any other a group.

The regional hospital board, he believed, had d excellent work, and the number of beds available now probably sufficient, but the proper use of the b was handicapped by lack of nurses. Mr. Short was a anxious that general practitioners should be gi better X-ray facilities at the clinics and more opp tunity for consultation with chest physicians, and felt that local authorities should be more active aftercare.

Miss PATRICIA HORNSBY-SMITH, parliamentary se tary to the Ministry of Health, did not wholly accept implications which Mr. Short had drawn from some of figures he had quoted. Though the incidence of tuber losis on Tyneside had been higher for many years th in other parts of the country, she thought it was fai point out that the number of deaths from tubercul on Tyneside were now half what they were 20 years a despite the greatly increased population. In 1945 Newcastle upon Tyne there were 227 deaths from resp tory tuberculosis, and in 1950, 183, a reduction o fifth. In Northumberland the figures in 1945 were 1 and in 1950, 124, a reduction of a third. The figure the whole of England and Wales over the same per showed a reduction of a third. Notifications were falling so fast, largely because more cases had b detected by mass radiography. The waiting-lists inpatient treatment were now much lower. Since Ju 1948, the Newcastle Regional Hospital Board had ope 561 additional beds. The number of patients not fou a bed within ten days had been reduced from 540 at end of 1950 to 420 at the end of 1951. Of the mass-radiography units in England and Wales 5 w operating in the area of the Newcastle Hospital Bo and were examining 170,000 people a year.

QUESTION TIME

National Health Service

Replying to a question, Mr. H. F. C. CROOKSHANK said th during 1951 in England and Wales about 220 million p scriptions were dispensed through the N.H.S. pharm ceutical service; 4·7 million pairs of spectacles were iss (excluding those supplied through the hospital servic and 10 million dental treatments, or courses of treatme were given.

M.R.C. Tests of New Tuberculosis Dru

In reply to a question Mr. JAMES STUART, Secretary State for Scotland, said that, under Medical Research Cou auspices, laboratory tests of isonicotinic acid hydra in the treatment of tuberculosis had already begun in t country.

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[1] Aspin, J. *Brit. med. J.* Feb. 9, 1952, p. 327.

[2] Hall, S., Tattersall, W. *Lancet*, 1950, i, 490.

[3] *Ibid*, p. 689.

[4] Kekwick, A., Paulley, J. W., Riches, E. W., Semple, R. *Brit. J. Urol.* 1951, 23, 112.

Obituary

CHARLES SCOTT SHERRINGTON

O.M., G.B.E., M.D., Sc.D. Camb., F.R.C.P., F.R.C.S., F.R.S.

Sir Charles Sherrington, the oldest member of the rder of Merit, past president of the Royal Society, and rmerly Waynflete professor of physiology in the niversity of Oxford, died at Eastbourne on March 4 t the age of 94. Though he disclaimed acquaintance ith clinical neurology, much of the treatment of nervous isorders and many of the principles of neurosurgery re based on his work. In his retirement, with the pen of poet and the brain of a scientist, he earned the honourble title of the Philosopher of the Nervous System.

[W. Thomas

Charles Sherrington was born n London, the son of James herrington of Yarmouth. His ather died when he was still oung, and he and his two rothers were brought up in he home of their stepfather, Dr. Caleb Rose of Ipswich. Rose inspired them with his wn interest in archæology and geology, and from his fine collection of paintings they learned to appreciate art. At Ipswich Grammar School Sherrington was taught little but the classics, and all his life he was a more than adequate Latinist. He once said himself that he grew up in a generation when "science was socially not quite the thing," and he learned no science until he joined his elder brother at Caius College, Cambridge, in 1881. There, under the stimulating tutelage of Sir Michael Foster, he began to study physiology. Even as an undergraduate he was engrossed in research, and his first short paper, with the long title of "On sections of the right half of the medulla oblongata and of the spinal cord of the dog which was exhibited by Professor Goltz at the International Medical Congress of 1881," appeared in the *Journal of Physiology* in 1884.

At first he intended to become a pathologist, and after taking his medical degree from St. Thomas's Hospital in 1885 he accompanied C. S. Roy to Spain as a member of the Royal Society's commission on Asiatic cholera. In the following year he visited Italy alone to continue this study, and later he rounded off these *Wanderjahre* by sojourns in the laboratories of Virchow and Koch in Berlin and of Goltz at Strasbourg.

On returning to London he was appointed lecturer in physiology at St. Thomas's Hospital, and in 1891 he succeeded Sir Victor Horsley as superintendent of the Brown Institution, a veterinary hospital of the University of London. Here he made full use of the experimental material at his disposal. From exhaustive studies of the distribution of the nerve-roots and sensory dermatomes he turned his attention to the sensory nerve-supply of muscles and to the reflex behaviour of antagonistic muscles. This series of classical investigations quickly gained recognition; in 1893 he was elected F.R.S. and in 1895 he was called to the chair of physiology at Liverpool. There his competence as a man of affairs, as well as his genius as a scientist, became clear. He organised the Thompson Yates Laboratory in new buildings, helped to start new departments of psychophysiology and veterinary medicine, and introduced a course on school hygiene. He also continued his studies of reciprocal innervation of antagonistic muscle, and to this period belong his papers on decerebrate rigidity. In 1904 he delivered the famous Silliman lectures at Yale University, which, when later published as *The Integrative Action of the Nervous System*, showed how through careful analysis of his observations he had built up constructive hypotheses and gradually converted them into what are now recognised physiological principles.

In 1913 Sherrington accepted an invitation to the Waynflete chair of physiology at Oxford. The setting and atmosphere were congenial to him, as he confessed in one of his verses:

> "Sworn Priest of Beauty, these
> thy shrines among,
> That kneelst with old folk and
> that dancest with young."

But only too soon after he arrived in Oxford his hopes of research were interrupted by the outbreak of war. Much of his time was taken up by work for Government bodies; he sat on a Home Office committee for the lighting of factories and workshops, a War Office commission on tetanus, and the scientific council of the Central Board for the Control of Alcoholism, and he became chairman of the Industrial Fatigue Research Board. Anxious to do still more, during the vacation he got a job as a workman—"unskilled, of course" he modestly explained—at a munition factory.

> "It was a motor-car works in time of peace," he wrote to a friend, "but now converted into a 3-inch shrapnel shell factory. I was there three months . . . on the day shift; the day shift hours were 7.30 A.M. to 8.30 P.M. every weekday and 8 to 5 on Sundays. We had one hour for dinner (in a canteen, sixpence a head, plenty of fair food, but such table-cloths! Their only pattern was spots of spilled victuals!), and one half-hour for tea-supper at 5.30 (fourpence)."

Once the war was over, with his customary effective tact, he persuaded the university to re-equip and rebuild his laboratories; and his stream of papers was resumed in the form of additions to his studies on the reflexes, on cortical localisation, on the discharge mechanisms of the nervous impulse, and on the stretch reflex. When he retired from his chair in 1936 his intellectual curiosity was as discerning as ever. As Sir Geoffrey Jefferson has put it, he knew what questions could be asked on Nature and what could not.

The collection of honours that fell to Sherrington was almost as remarkable as the career that occasioned them. He held honorary degrees from 22 universities, ranging from Liverpool to Athens and from Uppsala to Montreal. He was president of the Royal Society from 1920 to 1925. He was created O.M. in 1924 and G.B.E. in 1932. The same year, jointly with Prof. E. D. Adrian, he was awarded the Nobel prize for medicine. Alongside these luminous national distinctions there glowed with smaller but no less friendly light the tributes of his colleagues—he held the Royal and Copley medals of the Royal Society, the Baly gold medal and the Conway Evans prize of the Royal College of Physicians, the Retzius gold medal of the Swedish Academy, and the Hughlings Jackson medal of the Royal Society of Medicine. Besides these formal awards he also received the spontaneous tributes which are inspired by affection as well as admiration. Thus an edition of his *Selected Writings* was sponsored by the guarantors of *Brain*, and for the International Physiological Congress held in Oxford in 1947 the Physiological Society had reprinted a new edition of his *Integrative Action of the Nervous System*, in the belief that members of the congress "both for sentimental and practical reasons would be glad to possess a copy."

Until he was separated from his laboratory, Sherrington remained the detached scientific observer and recorder. With his Gifford lectures to the University of Edinburgh in 1936–38 (republished as *Man on His Nature* in 1940) he began the considered evaluation of the implications of his own work which was to be the fruit of his old age. In these lectures he illustrated the astonishing journey the mind of man has made by contrasting modern knowledge with the intelligent, but often inaccurate, guesses forced upon Jean Fernel in the 16th century. The *Endeavour of Jean Fernel* (1946) is an attractive pendant to the larger work. A second edition of his small but choice harvest of poems, *Assaying of Brabantius*, appeared in 1940. To Sherrington's years of research we owe a wealth of careful observation, elegant demonstration, and fruitful synthesis. To his years of reflection we owe his assessment of what remains unknown, and his assertion that mind remains apart—supreme and untouched. In his own words:

> "mind for anything perception can compass, goes therefore in our spatial world more ghostly than a ghost. Invisible, intangible, it is a thing not even of outline; it is not a 'thing.' It remains without sensual confirmation, and remains without it for ever. Stripped to nakedness there remains to it but itself. What then does that amount to? All that counts in life. Desire, zest, truth, love, knowledge, 'values,' and, seeking metaphor to eke out expression, hell's depth and heaven's utmost height. Naked mind."

J. C. E. writes: "As I meditate on the death of Sherrington, I am carried back to many happy and rich experiences, ranging from a long conversation only nine days before he died to my first Sunday afternoon tea at the Sherrington home in October, 1925. That was the first of a long series of delightful memories, for Sir Charles and Lady Sherrington were at home to students every Sunday afternoon, and students from the Empire-overseas were given a special welcome. He was an amazing conversationalist with a flow of ideas, stories, and experiences coming often faster than he could express them. Then I remember the night that the Nobel award was announced. Sir Charles had heard the news in the afternoon, but went to Merton College to dine and kept the secret. It was announced later over the air, and he returned home to find his friends already there. We drank his health in sherry! That was the last happy occasion I can remember in his home, for Lady Sherrington fell ill and died some months later.

"Sherrington lived an amazingly intense intellectual life, overflowing with ideas and imagery. Even at the end, in extreme old age, his mind went questing for truth. He wanted no superficial solutions, realising as he did the immense complexity of Nature and the mystery of existence. He was remarkable as one who accepted the validity of the whole experience; the direct experience of 'one's self' as well as the perceptual experience mediated by sense organs. His book *Man on His Nature* is an exhaustive attempt at the complete understanding of man. Despite minor defects, that book is great by any standards, and it should rank as a classic with the *Integrative Action of the Nervous System*, each creating a new epoch of thought. Just as the *Integrative Action* has modelled our thinking and research on the central nervous system for nearly fifty years, so it may be predicted that *Man on His Nature* will reorientate scientific thinking on man himself. T Sherrington man was dualistic in nature, both and mind, and mind amounts to 'all that counts in life.'

From an American colleague we have received tl following tribute:

Sir Charles Sherrington, writes J. F. F., has been living force for more than sixty years; not only has guided the course of neurophysiology, but he h influenced the whole field of scientific medicine. H pupils came to him from all parts of the world, and still larger body who never knew him have been pr foundly influenced by his writings. From this side the Atlantic he had a series of loyal followers beginni with Harvey Cushing who went to Liverpool in 19 when Sherrington was just beginning his series notable studies with Grünbaum on the anthropoid bra Cushing had come at an ideal moment, for he was al to assist with the craniotomies in several chimpanzees large orang, and a famous female gorilla—the anim which Sir Charles discovered one day peering at h through the keyhole of the cage when he was attempti to peer at her from the other side. Cushing also had artistic flair and his freehand sketch of the gorilla mot area was much appreciated by Professor Sherringt and was later used (in 1917) when he and Grünbau (Leyton) came to publish their celebrated paper on t anthropoid cortex.

Since then there have been many other American a Canadian students, the late R. S. Woodworth, Alexand Forbes, Wilder Penfield, the late Cuthbert Bazel Henry Viets, and, after the first world war, a group younger men, all of whom now also occupy importa chairs, Stanley Cobb (Harvard Medical School), Hebbel Hoff (Baylor University), his brother Ebbe C. H (Medical College of Virginia), Theodore C. Ruch (U versity of Washington), and Derek Denny-Brown of N Zealand, now professor of neurology at the Harva Medical School—these and many others such as Grays McCouch, David Rioch, and Franc Ingraham.

My own relationship with Sir Charles began in 1 when I went up to Oxford as a Rhodes scholar, a although more than thirty years have since elapsed can only say again what I said in my Sherrington lect given in Liverpool last October, that the spell cast Sir Charles remains as vivid now as then.

Many anecdotes about his early years that he was w to tell from time to time come easily to mind: his expedit in 1885 to investigate a cholera epidemic in Spain where had difficulty at first with the clergy in securing permiss for autopsies—a difficulty he eventually solved by having old priest do the autopsies for him; his experiences in laboratories of Koch, Waldeyer, Virchow, Cohnheim, later of Goltz. Goltz, he related, came down from his apa ment to the student lecture-room in his bed slippers at eig o'clock in order to get the students off his mind as early the day as possible. When Sherrington left Goltz's laborato as an act of grace he made the gruff old gentleman a pres of three monkeys. Goltz never spoke to him again, becau he thought the brash young Englishman was trying persuade him of the existence of functional localisation in t cortex, a dogma to which he violently objected.

Another anecdote might be told of his retirement fr Oxford in 1935. He summoned me to his room and wit slightly apologetic expression showed me some forty medi incunabula stored away in the back of a large drawer. Wit smile and twinkle that all book collectors will understand, said, "Dear Ethel, my devoted wife, doesn't fully share interests in incunabula and I am passing them on to t British Museum." Lady Sherrington was a remarka woman who aided Sir Charles in everything he did, and I f sure that had his sense of guilt over the amount he h invested in his 15th century books not prevented him fr showing them to her, she would have shared his enthusiasm although perhaps wrily—for these as for his many oth interests. Students had the same sense of deep affection her as they did for him, for she was untiring in the attentio which she extended to them and to their wives.

Sir Charles's broad philosophy can perhaps best gleaned from a few terse sentences of the preface the second edition of *Man on His Nature*:

This edition has given opportunity for a certain amount revision as regards detail. The book stresses the view th is a product, like so much else, of the play of natural s acting on the material and under the conditions past present obtaining on the surface of our planet. If the succeeds in drawing sympathetic attention to this theme ose who read it, its pages will have handsomely rewarded of the best hopes of its author.

r Charles married in 1892 Miss Ethel Wright. She in 1933. They are survived by their only son.

Diary of the Week

MARCH 16 TO 22

iday, 17th

TERIAN SOCIETY
.M. (Talbot Restaurant, London Wall, E.C.2.) Prof. Lambert Rogers, Dr. John Spillane: Contribution of Surgery to Neurology.

sday, 18th

AL COLLEGE OF SURGEONS, Lincoln's Inn Fields, W.C.2
P.M. Mr. M. F. A. Woodruff: Transplantation of Homologous Tissue. (Hunterian lecture.)
ISH POSTGRADUATE MEDICAL FEDERATION
30 P.M. (London School of Hygiene, Keppel Street, W.C.1.) Prof. W. V. Mayneord, D.SC: Physical Techniques in the Medical Applications of Ionising Radiations.
ITUTE OF DERMATOLOGY, St. John's Hospital, Lisle Street, W.C.2
30 P.M. Dr. S. Thomson: Parasitic Diseases.
ENICS SOCIETY
30 P.M. (Royal Society, Burlington House, W.1.) Mr. A. J. Brayshaw, B.A.: Stability of Marriage.

dnesday, 19th

AL COLLEGE OF SURGEONS
P.M. Prof. R. R. Macintosh: Antecedents of Early Anæsthetic Apparatus. (Joseph Clover lecture.)
AL SOCIETY OF MEDICINE, 1, Wimpole Street, W.1
P.M. *Section of Comparative Medicine.* Prof. R. E. Glover, B.SC., Dr. S. D. Elek, Dr. P. Stuart: Acid-fast Bacilli Cultivation and Diagnostic Procedures.
.15 P.M. *Section of General Practice.* Dr. S. R. Wood: Out Damned Spot.
TITUTE OF DERMATOLOGY
.30 P.M. Dr. J. O. Oliver: Immunology in Relation to Dermatology.
YAL INSTITUTE OF PUBLIC HEALTH AND HYGIENE, 28, Portland Place, W.1
.30 P.M. Dr. R. W. Barr-Brown: First-aid in the Home.
TH WEST LONDON MEDICAL SOCIETY
.30 P.M. (Bolingbroke Hospital, Wandsworth Common, S.W.11.) Dr. W. J. O'Donovan: Modern Skins and Modern Drugs.
DLAND MEDICAL SOCIETY
.15 P.M. (Birmingham Medical Institute, 154, Great Charles Street, Birmingham, 3.) Prof. T. L. Hardy, Mr. B. N. Brooke: Ulcerative Colitis.

ursday, 20th

YAL COLLEGE OF SURGEONS
P.M. Mr. G. R. Fisk: Hyperplasia and Metaplasia in Synovial Membrane. (Hunterian lecture.)
ITISH POSTGRADUATE MEDICAL FEDERATION
.30 P.M. (London School of Hygiene.) Dr. J. F. Loutit: Biological Effects of Radiation.
ITISH INSTITUTE OF RADIOLOGY, 32, Welbeck Street, W.1
P.M. Dr. B. Jolles: The Sieve in Radiotherapy.
STITUTE OF CHILD HEALTH, The Hospital for Sick Children, Great Ormond Street, W.C.1
P.M. Mr. T. T. Higgins: Genito-urinary Surgery.
YAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE
.30 P.M. (Royal Army Medical College, Millbank, S.W.1.) Laboratory meeting.
VERPOOL MEDICAL INSTITUTION
2.30 P.M. (County Hospital, Whiston, near Prescot, Lancs.) Clinical demonstration.

iday, 21st

YAL SOCIETY OF MEDICINE
4.30 P.M. *Section of Epidemiology and State Medicine.* Sir Alan Rook, Dr. T. A. Lloyd-Davies, Major M. M. Lewis: Health—Its Study and Culture in the Nation Today.
8.15 P.M. *Section of Radiology.* Dr. James Sommerville, Dr. A. A. Charteris: Radiotherapy in the Treatment of Simple Skin Conditions.
ACULTY OF RADIOLOGISTS
4 P.M. *Radiotherapy section.* (Royal College of Surgeons.) Mr. J. Scott Tough: Application of Plastic Surgery to Radiotherapy.
STITUTE OF DERMATOLOGY
5.30 P.M. Dr. E. J. Moynahan: Clinical demonstration.
STITUTE OF DISEASES OF THE CHEST AND INSTITUTE OF CARDIOLOGY
5.30 P.M. (London School of Hygiene.) Mr. Norman Barrett: Cardiac Trauma.
. GEORGE'S HOSPITAL MEDICAL SCHOOL, Hyde Park Corner, S.W.1
5 P.M. Prof. J. G. G. Borst (Amsterdam): Nocturia—A Defeat in the Battle Against Gravity. (Thomas Young lecture.)
IOCHEMICAL SOCIETY
10.30 A.M. (National Institute for Medical Research, Mill Hill, N.W.7.) Scientific papers.
MIDDLESEX COUNTY MEDICAL SOCIETY
3 P.M. (Hillingdon Hospital, Uxbridge.) Mr. F. Boyes Korkis: Pharyngeal Diverticulum.

Saturday, 22nd

NUTRITION SOCIETY
10.30 A.M. (University of Manchester.) Symposium on Diet in Relation to Renal and Cardiovascular Disease.

Notes and News

A NEW UNIT AT U.C.H.

TREATMENT *and research are being very profitably combined* in the new metabolism and radio-isotope unit at University College Hospital, where the difficulties of putting a new idea into practice have been skilfully overcome. A children's ward has been completely reconstructed to accommodate eight patients and all the equipment needed for their metabolic investigation or the study of their reaction to radioactive isotopes. The particular merit of the unit lies in the compact way in which its necessary parts have been brought together to give a considerable degree of independence.

This autonomy is especially important in the metabolic work, directed by Prof. M. L. Rosenheim. The day-to-day laboratory investigations are carried out in the unit's own laboratory by its own biochemists—an arrangement which minimises the inaccuracies of personal error. A more scrupulous account can be kept of the intake and output of each patient, and diet can be more rigorously controlled, than is usually possible in a general ward. A dietitian plans each diet to meet the needs of the particular investigation, and it is then prepared in a special kitchen set aside for the purpose. The patients are put through their metabolic paces in pleasant surroundings. The small wards are enlivened by the attractive murals designed for the original occupants.

Dr. E. E. Pochin is in charge of the work with radioisotopes. His patients usually join those of Professor Rosenheim in the wards. The γ-counting room, where the uptake of radio-iodine in malignant and toxic thyroid glands is measured, has been carefully set apart to ensure that radioactive material enters it only in the body of a patient. The treatment room is ingeniously equipped for the safe handling of the isotopes by remote control. Massive lead protection is unnecessary if the lesson of the inverse square law—the further away the better—is properly applied as it is here. Radioactive excretion is measured by a bank of counters in another room. Urine is then stored behind lead until its radioactivity has decayed to a level at which it may safely be discarded. Dr. Pochin points out that the work is following the same general lines as that in other centres. But, a visitor might remark, there can be few of them so suitably housed.

Much care and thought have gone into the design and organisation of the unit, which is in the immediate care of Dr. C. E. Dent. Valuable results will certainly come from both its halves.

ISONICOTINIC ACID DERIVATIVES IN TUBERCULOSIS

OUR annotation of March 1 (p. 454) mentioned that isonicotinic acid hydrazine is now under trial in this country. We understand that investigations are already being made with substantial quantities of the drug supplied by at least three manufacturers, and that arrangements are in hand for producing it in large amounts if it fulfils the promise of early reports (see p. 547). It will be distributed by Roche Products Ltd. under the name of 'Rimifon'; by E. R. Squibb & Sons under the name of 'Nydrazid'; and by Herts Pharmaceuticals Ltd. under the name of 'Pycazide.' Related work on the tuberculostatic activity of thiosemicarbazone derivatives has been published in the past year or two from the research department of the last-mentioned firm (see *J. Pharm. Pharmacol.* 1950, 2, 759, 764.)

TONSILS AND ADENOIDS

AT a meeting of the Devon and Exeter Medico-Chirurgical Society on Jan. 24, Mr. Raymond Hinde discussed "dogmas and doubts" about tonsils and adenoids. Changes in the tonsils at the time of the first dentition, he said, are more often caused by a physiological hyperplasia than by infection. *It is impossible to tell whether a tonsil is septic or not merely* by looking at it. A swab from the tonsils is never sterile since tonsillar crypts normally contain food debris and organisms; only when a crypt becomes sealed off does it become a source of sepsis.

Mr. Hinde thought it by no means certain that adenoids may cause frequent colds. They should be removed only if they obstruct respiration or if they are a source of infection.

Even then it is advisable to wait at least six months to ensure that the enlargement is really pathological. On the score of mere size tonsils should be removed only if they meet in the midline or cause dysphagia. He laid stress on the importance of complete removal; remnants may cause more trouble than a whole tonsil. When operation has been decided on, the best time for it is when the child has been at school for six or nine months and has been able to develop such immunity as he can to the organisms to which he is exposed.

It may be difficult or impossible to correct the faults of environment and home hygiene, but in a family where there are several children it is possible—and sensible—to treat the child who starts the attacks and leave the others alone.

INFECTIVE HEPATITIS AMONG SURGEONS

IN Sweden, where infective hepatitis has been notifiable since 1931, the incidence of the disease has been rising. In the period 1931–37 notifications numbered 1300 yearly. In the period 1943–46 the number rose to some 7000 a year; and in 1947 and 1948 notifications numbered 8554 and 11,736. Epidemics of jaundice have been most noticeable in the two largest towns, and during the last couple of years it has been necessary to provide for such cases a special department, with some 100 beds, at the infectious-diseases hospital in Stockholm. Suspecting that the hepatitis-rate may be exceptionally high in those doctors who are most often in direct contact with the blood of their fellow-beings, Dr. J. P. Strömbeck[1] has circularised the members of the Swedish Medical Association—4030 in all—asking them whether and when they have suffered from jaundice. He has classified them in three groups: (1) general practitioners; (2) hospital doctors without operative duties (physicians, radiologists, &c.); and (3) hospital doctors with operative duties (general surgeons, aural surgeons, obstetricians, gynæcologists, dental surgeons, &c.). Answers were given by 3802, or 94·3%. It was found that the jaundice-rate was lowest among the general practitioners and highest among the hospital doctors who undertook operations; but the difference between the two hospital categories was not statistically significant, and indeed the pitfalls inherent in such a comparison are so great that its value is questionable. In Denmark Dr. Sten Madsen has circularised some 4700 doctors on the subject and has obtained answers from 94%. It would seem that the hepatitis-rate is higher among Danish than among Swedish doctors. In both countries the rate for doctors is comparatively high after the age of 25. Dr. Madsen is planning a similar inquiry in the legal profession, as he presumes that lawyers may serve as useful controls.

INDIA'S INSURANCE SCHEME

AN insurance scheme for industrial workers in India was inaugurated on Feb. 24. Its ultimate aim is to cover 2,500,000 workers, but in the first instance it is available to 150,000 in Delhi and Kanpur. Employees will get sickness, maternity, disablement, and dependant benefits and free medical care. Sickness benefit, equal to half the average wage, is payable for up to eight weeks in one year. The maternity benefit is 12 annas per day or the sickness-benefit rate, whichever is higher, and may be paid for up to twelve weeks, of which not more than six can precede the confinement. Persons disabled by injury at work will now receive pensions; previously they had been given lump sums and the less provident soon fell upon hard times.

Workers earning less than a rupee a day are exempt from contributions; those earning more than one and a half rupees will contribute a little over 2% of their wages, and the employers 1¼% of their total wage bill towards financing the scheme.

The medical service has 10 dispensaries, including a mobile unit, in Delhi and 13 in Kanpur. The scheme will be gradually extended to other regions; it will be introduced in 11 industrial centres in the Punjab in August, and in Bombay, Madras, Calcutta, and elsewhere next year.

The Indian scheme differs from our own in its graded contributions and benefits. Everyone in Britain is now insured, but it took nearly forty years for such a comprehensive plan to evolve. The Indian service aims to reach its first target of 2,500,000 in four or five years, and the Employees' State Insurance Act of 1948 allows for the extension of the scheme to all types of employee in due course.

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[1] *Svenska Läkartidn.* Feb. 1, 1952, p. 265.

NEW RHEUMATISM CLINIC

A CLINIC has been opened near Gerrards Cross with accommodation for 26 patients suffering from rheumatism or allied diseases. A few beds will be available to nurses and medical students at reduced fees. A resident doctor will be in [illegible] of day-to-day treatment; the visiting consultant physicians are Dr. W. S. Tegner and Dr. F. Dudley Hart; and the consulting staff are Sir Horace Evans, Mr. H. E. Harding, Miss Gladys Hill, Mr. E. R. G. Passe, and Miss Helen Mayo. Miss D. Anderton Sharpe, F.R.C.S., is the managing director. Further particulars may be had from the secretary of Chalfont Lodge Clinic, Gerrards Cross, Bucks.

A PERSONAL ANTHOLOGY

AN anthology, as Sir Russell Brain reminds us in a foreword to Dr. Robert Coope's book,[1] is a collection of flowers. And since no two people ever gather the same nosegay, anthologies have a double charm, permitting us to admire the choice and arrangement while we speculate on the nature of the chooser. *The Quiet Art*, as its title suggests, is in the main a grave and tranquil little book; but its colours, though muted, are not dull. These writings about medicine are drawn from both the ancients and the moderns, from doctors and laymen; they tell of disease and the cure of disease, of the men who worked to overcome this ill or that, of cancer, of the old and the dying, of children, of patients and the wisdom and wit of patients (particularly Sydney Smith), of curiosities of treatment (thus the first use of rubber tubing to drain an abscess was made by Lister on Queen Victoria), of quacks, of fashions, and of faith. Many of the quotations show how well some doctors used to write, and a few still do: quite as well in most cases as the poets, philosophers, biographers, novelists, journalists, prophets, and saints who are the remaining contributors. He will be hard to please who does not hear among this host of voices one or two calling to him personally, or encounter a memorable saying to light up his own experience or thought. The volume fails as a pillow-book, being apt to keep one awake.

MEDICAL SUPERVISION IN NORWEGIAN INDUSTRIES

SOON after the late war the Norwegian Medical Association, the Norwegian Employers' Association, and the Norwegian Labour Party agreed to promote a scheme for the medical supervision of industrial concerns and certain government services. The triple object of this scheme,[2] sponsored by Prof. Axel Ström and Prof. Haakon Natvig among others, is to discover hitherto unknown cases of disease, to give timely advice on health problems, and to provide information on the frequency of certain diseases; and by the autumn of 1951 the scheme was in operation in 540 industrial and other concerns employing some 164,000 clerical and manual workers. Professor Natvig[2] reports that in the course of 37,896 examinations in 1949 tuberculosis was found in 500 cases, in 81 of which no medical treatment had hitherto been given. During the same year 100 cases of venereal disease were discovered, and 62 of these cases had hitherto been untreated. He has calculated that among the people coming under this scheme one may expect to find each year 350 cases of tuberculosis, 250 cases of syphilis, and 110 cases of cancer, besides other ailments liable to be overlooked for want of a systematic search.

DE CONSERVANDA VALETUDINE

DEPLORE it or not, books on how to keep well are not much read by the general practitioner. What time he has for serious reading is fully occupied in keeping abreast of curative medicine, which, he feels, is really his job. A few specific measures against infectious diseases (inoculations, isolation, disinfection, and so on), a little advice to new mothers, and to older ones when they or their children are approaching some crisis—that is all the preventive medicine that the doctor's customers expect, or indeed will accept with any gratitude. Nevertheless, the medical librarian must occasionally receive sheepish but urgent requests for popular books on health from doctors who have promised to talk to the local Women's Institute or Toc H, or to write for the parish magazine, and realise too late how little they know about health. For such emergencies each librarian no doubt compiles his own list. The more erudite may be ed, like this note, with the title of the 17th century a work of Fabricius Hildanus, of Berne—a little book rkable for its flowery dedication to the author's noble on, whose name, in 24-point capitals, swamps the title- almost to the exclusion of the author's. Among the y modern books to choose from, the second edition of late Dr. Harry Roberts's *Everyman in Health and Sickness,* sed by Dr. Margaret N. Jackson, is expected shortly, and be safely recommended. And those who want "something rent" will find a great deal of sense, backed by facts figures, in *Your Health,* by Prof. D. F. Smiley and . A. G. Gould, of Cornell (Macmillan, 1951, pp. 555, 34*s*.).

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[1] The Quiet Art. A Doctor's Anthology. Edinburgh: E. & S. Livingstone. 1952. Pp. 284. 12s. 6d.

[2] *Nord. Med.* Feb. 1, 1952, pp. 141–144.

FILM ON CARDIAC OUTPUT

s Feb. 13 at a meeting of the Scientific Film Association Westminster Hospital, *Cardiac Output in Man* (16 mm., nd, colour, 38 min.) was shown. This film, which was made I.C.I. in collaboration with the staff of the department medicine of the Postgraduate Medical School of London, lains the principles of the estimation of cardiac output by Fick principle and by the Hamilton dye method. It shows development of cardiac catheterisation by Forssmann l the technique used by McMichael at the Postgraduate dical School. The technique of the dye method is then wn and the results of the two methods compared.

he main criticism of the audience was a lack of balance in the nts emphasised. Too much time was spent showing detailed nts of technique, such as the injection of a local anæsthetic over vin, while the practical applications of the results were hardly ntioned. Greater use might have been made of symbolic diagrams, the realistic illustrations used were sometimes a rather confusing kground to the commentary. The standard of photography in eral was high, but the shots of graphs were poor and the cineradio- phs of the catheter in the heart were hard to follow. But the dience agreed that the subject was difficult to put over effectively, d they congratulated the producers on the high standard they d achieved.

PONGOS

About 1590 an English seaman named Andrew Battel, o had spent some time in the wilds of West Africa, gave the orld the first account of the pongo or gorilla; but nothing ore was heard until 1846, when Dr. Thomas Savage, a issionary, found a skull of a gorilla; he sent a sketch of it Sir Richard Owen in 1847. A little later Paul du Chaillu, ho wrote equally enthrallingly about the northern anti- uities of the Vikings, introduced the pongo, in his popular ook on gorilla-hunting in equatorial Africa, to the man in e street. In 1855 a live young female gorilla (mistaken for chimpanzee) was kept in Wombwell's travelling menagerie England, and when she died she was stuffed by Charles aterton, that eccentric naturalist who first introduced rare and the Little Owl into England. In 1903 only one e gorilla (a baby) had ever landed in U.S.A., and it survived ly five days. Since then the number of gorillas in Europe as dwindled and that in the U.S.A. increased until in 1949 the tter country contained 25.[1] The catching of baby gorillas as become such a trade that Yerkes[2] has made another ensus in the U.S.A. and reached a total of 44 gorillas in aptivity. He laments, however, that very little scientific se is made of all this material, and that the genus is bound to ie out, probably within a century, because it has no chance f survival in competition with man, especially since, to apture the young, the hunters slay the parents. The gorilla s an example of a genus too much adapted to special cir- umstances to be able to survive when those circumstances re eliminated.

IRISH APPOINTMENTS

Dr. P. J. Delaney, medical secretary of the Irish Medical ssociation, informs us that the council of the association has been considering the terms of service of the recently dvertised position of county surgeon at Waterford.

The council has decided that the appointment should be black- sted because the conditions of service prevent private practice xcept to an extremely limited degree and then only in respect of rivate patients in State hospitals. Dr. Delaney adds that "there e other very objectionable features to this appointment."

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mployment of Older Men and Women

The members of the National Advisory Committee on the mployment of Older Men and Women include Dr. G. E. odber and Dr. E. R. A. Merewether.

University of Oxford

On March 1 the following degrees were conferred:

D.M.—W. H. H. Andrews, R. I. K. Elliott, H. A. W. Forbes, *Anthony Batty-Shaw, *E. A. Spriggs.

B.M.—*Pauline O'Neill.

*In absentia.

University of London

At a recent examination for the academic postgraduate diploma in medical radiology (diagnosis) the following were successful in part I:

D. A. B. Ashcroft, Aaron Berezowski, M. E. Berk, A. S. Bligh, Donald Brink, N. L. Bucky, Hassan Fateh, B. C. Hale, M. A. Harris, Kantilal Nagardas Kamdar, J. K. Lundie, G. A. Medhurst, J. L. Morris, D. M. K. Muir, I. A. H. Munro, Elias Price, L. J. Sandell, J. V. Tillett, L. E. Wolpert, Manuel Ziman, Irvan Yentis.

Royal College of Physicians of Ireland

On March 7, Dr. Eleanor B. Outon was admitted, in absentia, as a licentiate and member of the college.

Scottish Conjoint Board

On March 8 the following, having passed the final examination, were admitted licentiates of the Royal Colleges of Physicians and Surgeons of Edinburgh, and the Royal Faculty of Physicians and Surgeons of Glasgow:

J. C. Aickin, I. S. Arthur, Timothy Awuku-Asabre, J. H. Beatty, Joseph Berlow, W. N. Brady, C. M. S. Calder, D. I. Cowan, John Davies, Valerie P. Fogg, Alexander Baba Gwan-Nulla, Mary Iball, Agnes Kramer, Catherine S. MacGregor, Ivan MacIntyre, Cecily R. Murray, Eileen Reddy, Ferenc Sandor, William Scott, Sheila Sweeney, A. C. Thomson, Walter Welsh, Joan W. Whitaker, S. M. Young.

Ophthalmological Society of the United Kingdom

The annual congress of this society will be held at the Royal College of Surgeons in Ireland, Dublin, on Thursday, Friday, and Saturday, April 17, 18, and 19, under the presidency of Mr. M. H. Whiting. The programme will include a discussion on the Value of Cortisone and A.C.T.H. in Ocular Diseases, when the opening speakers will be Prof. Alan Woods, Prof. H. F. Moore, Dr. F. S. Lavery, and Mr. E. G. Mackie. Prof. Derrick Vail will deliver the Montgomery lecture on Diffuse Collagenous Diseases with Ocular Complications.

Nan Williams Fund for Research in Leukæmia

A fund for research in leukæmia has been inaugurated by a gift of £1000 by the Rev. Emlyn Williams, a naval chaplain whose wife died recently of acute leukæmia. Those wishing to contribute to this fund should communicate with the registrar, University Registry, Oxford.

Caernarvonshire and Anglesey Pædiatric Club

This club was formed in 1950 to encourage discussions on infant care and management among medical and lay people interested in pædiatrics. Further information may be had from the secretary, Dr. G. W. Roberts, St. Fillans, Segontium Road South, Caernarvon.

Medical Association for Prevention of War

The inaugural meeting of the London and Home Counties branch of this association will be held at 8 P.M. on Thursday, March 20, at Friends House, Euston Road, N.W.1, when Mr. E. H. S. Burhop, PH.D., will speak on Atomic Physics in the Cause of Peace.

Medical Society of London

At a dinner on March 6 celebrating its 172nd anniversary, Lord Radcliffe sketched a background to the life of John Coakley Lettsom, physician, benefactor, and founder of this ancient society, and gave a charming account of the gardens and broad uplands of Camberwell Grove, now topographically rather different. In his response Mr. A. C. Palmer, the president, spoke with admiration of the efforts of those who had made such remarkable advances in medicine and surgery during his term of office, and contemplated with something akin to apprehension the marvels of transformation and creation which may soon be possible. Dr. W. G. Oakley, welcoming The Guests, recalled Sir Hugh Lett's series of 1000 cases of appendicitis collected at a time when knowledge of the disease was in its infancy. Sir Hugh, responding, told how the series was compiled at the London Hospital on the instruction of his chief, Sir Frederick Treves.

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[1] Riess, B. F., Ross, S., Lyerly, S. B., Birch, H. G. *Zoologica,* 1949, 34, 111.

[2] Yerkes, R. M. *J. Mammalogy,* 1951, 32, 429.

Auxiliary Royal Army Medical Funds

The annual general meeting of members of the Funds will be held at 11, Chandos Street, London, W.1, on Monday, April 7, at 5 P.M.

Australian Honours

For non-operational services in Japan in connection with operations in Korea, Colonel C. W. Nye, M.B. Melb., R.A.A.M.C., has been appointed O.B.E., and Major J. W. F. Lloyd, R.A.A.M.C., M.B.E.

International Hæmophilia Society

The annual general meeting of this society will be held on Sunday, April 20, at 2 P.M. at St. Pancras Town Hall, Euston Road, London, W.C.1. Further particulars may be had from 94, Southwark Bridge Road, London, S.E.1.

On Finding the Ministry of Health

The Ministry of Health has issued a reminder that all letters to the Department in London should be addressed to Savile Row, W.1, and not to Whitehall. Although the Ministry changed its address over eight months ago, 40% of letters are still wrongly addressed.

Blood Donors

Last year nearly 600,000 gifts of blood were made to hospitals in England and Wales through the National Blood Transfusion Service. This was 70,000 more than in 1950. During the year 114,000 new donors were enrolled, bringing the total strength to over 465,000; but another 170,000 are still needed.

World Veterans' Federation

This federation, formed in 1950, operates under the United Nations, and so far ex-Servicemen in 14 countries are represented; British ex-Servicemen's organisations are not yet represented. The federation's chief aim is the reablement of handicapped veterans; and Dr. Harold Balme, consultant advisor on rehabilitation to the United Nations and W.H.O., has accepted a similar appointment with this body. The federation is to hold a conference next month in Paris.

British Standard for Sintered Disc Filters

The British standard for sintered disc filters for laboratory use (B.S. 1752/1952) has been prepared with two aims: (*a*) to define a satisfactory filter for general use; and (*b*) to specify requirements which can be satisfied in the normal course of manufacture, and which will therefore not add appreciably to the cost. Copies of this standard may be obtained (price 2*s*.) from the British Standards Institution, Sales Branch, 24, Victoria Street, London, S.W.1.

British Pharmaceutical Exports

In terms of pounds sterling, the British pharmaceutical industry last year increased their exports of drugs, medicines, and medicinal preparations by nearly 50%, as the following figures show:

	£	*% increase on previous year*
1938	3,280,977 ..	..
1949	18,366,503 ..	16·04
1950	22,324,980 ..	21·55
1951	32,965,681 ..	47·66

Time-limits for Claiming Benefits

The National Insurance Advisory Committee, under the chairmanship of Sir Will Spens, has reviewed the time-limits for claiming benefits and for obtaining payment. It has recommended to the Minister that the time-limit for an individual claim to death grant and maternity attendance allowance should be extended from one month to three months; and that notice of retirement, at present required before a pension can begin, should be accepted up to one month after stopping work. No change is suggested in the time-limits for claiming sickness and unemployment benefits, nor in the rule which prevents retrospective awards of benefit for any period more than six months before the date of claim. The committee advises that awards already authorised should be payable for up to six months in all cases; under existing regulations the limit is three months, which may be extended to six months if good cause for the delay can be given.

Society of Public Analysts and other Analytical Chemists

A meeting of the biological methods group of this society will be held on Friday, March 14, at 6.30 P.M. at the Chemical Society's rooms, Burlington House, Piccadilly, London, W.1, to discuss the assay of coagulants and anticoagulants.

EMERGENCY BED SERVICE.—In the week ended last Monday applications for general acute cases numbered 1176. The proportion admitted was 87·1%.

The ninth edition of the Speech Therapists' section of the National Register of Medical Auxiliary Services has been published. Copies will be sent free to doctors, hospitals, and local authorities who apply to the secretary of the board, B.M.A. House, Tavistock Square, London, W.C.1.

Dr. C. J. Hackett, director of the Wellcome Museum of Medical Science, left London on March 7 for Bangkok, to attend a W.H.O. symposium on yaws. Between March 14 and 30 he will visit Indonesia on behalf of W.H.O.

Births, Marriages, and Deaths

BIRTHS

ALBERTS.—On March 4, at Sarisbury Green, Hants, the wife of Dr. Frank Alberts, D.A.—a son.

ALEXANDER.—On Feb. 22, the wife of Dr. F. G. Alexander, of Small Heath, Birmingham—a daughter.

BLACK.—On Feb. 18, in Birmingham, Dr. Margaret Black (formerly Lawrence), the wife of Dr. Alan Black—a son.

CALVEY.—On March 1, the wife of Dr. H. C. Calvey, of Sevenoaks, Kent—a son.

HOUSTON.—On March 3, in London, Dr. Thelma Houston (née Cruickshank), the wife of Dr. J. C. Houston—a son.

PARRY.—On Feb. 27, at North Harrow, the wife of Dr. H. E. Parry—a son.

RIVLIN.—On March 9, in Liverpool, Dr. Mona V. Rivlin (née Harris), the wife of Dr. J. J. Rivlin—a son.

RIVLIN.—On March 6, in London, the wife of Dr. Stanley Rivlin—a son.

DEATHS

BROWNE.—On March 3, at Wells, Somerset, Ada Margaret Browne, L.S.A.

JONES.—On March 6, in London, Edmund Benjamin Jones, F.R.C.S., L.D.S., aged 83.

LEVERTON-SPRY.—On March 3, at St. Keverne, Cornwall, Edward Leverton-Spry, M.R.C.S., aged 72.

MARTYN.—On March 4, at Moulton, Lincs, Frank de Recourt Martyn, M.R.C.S.

MILLARD.—On March 7, at Leicester, Charles Killick Millard, M.D., D.Sc. Edin., aged 81.

SHERRINGTON.—On March 4, at Eastbourne, Charles Scott Sherrington, O.M., G.B.E., M.D. Camb., F.R.C.P., F.R.S., aged 94.

THOROLD.—On March 4, at Bath, William Grant Thorold, B.M. Oxfd., major, I.M.S. retd., aged 89.

Appointments

ANDERSON, D. A. R., M.B. St. And.: M.O., Barlinnie Prison, Glasgow.

BARCLAY, G. A., M.A., M.B. Camb., F.R.C.S.: part-time consultant surgeon, St. Andrew's Hospital, London.

* BROOKS, D. M., M.A., M.B. Dubl., F.R.C.S.I.: consultant surgeon, physiotherapy and rehabilitation departments, Royal National Orthopædic Hospital, London.

FURNIVAL, J. T., M.R.C.S., D.M.R.D.: asst. radiologist, Bradford A group and Keighley group of hospitals.

GRIFFIN, E. M., M.D. Camb.: appointed factory doctor, Uppingham district, Rutland.

HAWKSLEY, MARGARET, M.B. Lond., D.A.: consultant anæsthetist, The Hospital for Sick Children, Great Ormond Street, London.

HUTTON, JAMES, M.D. Edin., D.P.H.: borough M.O.H. and area M.O. to borough and county of the town of Poole, Dorset.

MARKS, JOSEPH, M.D. Lond., M.R.C.P., Dip. Bact.: consultant bacteriologist, Central Tuberculosis Laboratory, Cardiff.

MITCHELL-HEGGS, G. B., O.B.E., M.D. Lond., F.R.C.P.: consultant dermatologist, Royal Masonic Hospital, London.

ODELL, J. R., M.B. Lond., D.A.: consultant anæsthetist, Elizabeth Garrett Anderson Hospital, London.

REID, DAVID, M.B. Edin.: appointed factory doctor, Linlithgow district, West Lothian.

SANGSTER, A. J., M.D. Edin., D.M.R.: asst. radiologist, Raigmore Hospital, Inverness.

* Amended notice.

The Terms and Conditions of Service of Hospital Medical and Dental Staff apply to all N.H.S. hospital posts we advertise, unless otherwise stated. Canvassing disqualifies, but candidates may normally visit the hospital by appointment.

AN INTERPRETATION OF STATISTICAL TRENDS IN TUBERCULOSIS*

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M.D. Lond.
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(Concluded from p. 525)

THE main theme of my first lecture was an interpretation of the present peak of mortality in older age-groups of males, and my conclusion was that this high rate could be brought into better perspective if compared with the even higher rates of mortality and morbidity experienced by this group of men when young, rather than by contrasting it with the much lower rates being experienced by young adult males at the present time. An obvious question to raise is "Why has the same postponement of the age of greatest mortality not occurred in women?"

This question is not quite correctly posed, since I showed that there was, at the end of the last century, some postponement of the age at which the highest rate of mortality occurred in females, due to a similar cohort effect. The question for which we really require an answer is "Why was this postponement in women so comparatively transient?"

An important part of the answer to this lies in the statistical oddity that, if the rates are falling equally at all ages of cohorts, but are plotted graphically for calendar years, a fall in rate of given rapidity may lead to a shift of the peak of a rounded or plateau type of curve (such as that for males in 1851–60), whereas for the same rate of improvement no shift occurs of the peak of a more sharply peaked curve (such as that of females in this country in 1851–60). This is part of the explanation of the shift for males and not for females; but that it is not the whole explanation is shown by the behaviour of the ratio of male to female mortality-rates. No matter whether a fall in rate is occurring equally at all ages at the same time, or equally at ages of cohorts, this ratio should not be disturbed if the two sexes are equally affected. In fact there has been a steady increase in the male/female ratio from unity in 1851–60 to about 1·4/1 in 1931–40.

If, however, this ratio is studied for separate age-groups (figs. 11 and 12), ages up to 20 show little variation—i.e., the sexes have shared equally in the improvement in rate. Over the age of 44 the ratio shows a steady increase—i.e., the rates for females have improved more than those for males. Between the ages of 20 and 34 the ratio at first increased, but it has been falling since 1910 till now it is below its original level, whereas at the age of 35–44 there was first an increase followed by a period of no change. Although a fall occurring equally at all ages of cohorts can explain the shift of the peak of a rounded curve and not of a steeply peaked curve, the behaviour of the male/female ratio shows that the female rates have followed the cohort pattern less rigidly than have the male rates. Logan (1950) has already suggested this on the basis of a statistical analysis using a very laborious method.

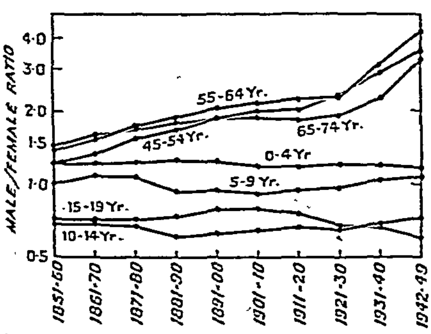

Fig. 11—Changes in ratio of male/female tuberculosis mortality rates in age-groups below 20 and above 44.

The explanation is, I believe, to be found in the different nature of tuberculosis in males and females. I suggested in the first lecture that the young adult mortality represents acute mortality, and I suggest that this more acute form of disease occurs in a greater proportion of cases in females than in males: this really is only another way of saying that young women are more susceptible than young men. In men, on the other hand, the disease tends to run a more chronic course with mortality spread over a longer period, and this will lead to a more obvious cohort effect among men than women.

I believe the differences in pattern of mortality between various countries are to be explained similarly: that is to say, in countries such as Ireland, Norway, and Sweden, with sharply peaked mortality curves for each sex, the course of tuberculosis is in the main more acute, leading to death after a shorter time, than in highly industrialised communities with more roundly peaked curves. One possible reason for this would be differences in racial susceptibility. Perhaps the populations of Ireland, Norway, and Sweden include more susceptible persons than do the more urbanised communities. Against this, is the fact that Copenhagen and Stockholm show the distribution of the industrialised countries, which suggests that it is not due to a racial characteristic but to an environmental one. That there are differences in racial susceptibility I have no doubt, as is shown by the American Negro and the Red Indian, but I doubt whether they explain the different types of mortality curve in Scandinavia and this country.

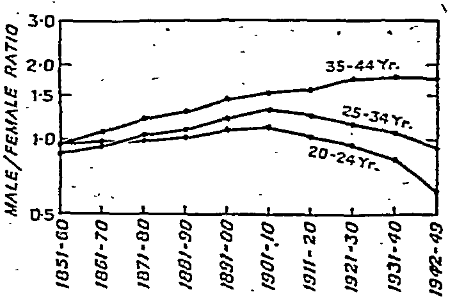

Fig. 12—Changes in ratio of male/female tuberculosis mortality rates in age-groups from 20 to 44.

Another explanation, and a purely environmental one, could be that under the conditions of urban life more cases occur, and these extra cases would be in persons with a little greater resistance in whom tuberculosis would run a rather longer course and lead to the death of some who, in more favourable rural conditions, might have survived.

Again, the discrepancy could be explained by a difference in the age at which primary tuberculous infection was predominantly occurring. It is now generally accepted that pulmonary tuberculosis is more common in uninfected persons exposed to infection than in infected persons similarly exposed, and, further, that the course of the disease is more acute after primary infection. There is much Scandinavian work to suggest that, in those countries, pulmonary tuberculosis is predominantly a disease following fairly soon after primary infection. If there has for decades been a considerable number of primary infections in young adults in those countries, this would be sufficient to account for the sharply peaked mortality curves compared with the more rounded curves of this country.

Shift of Peak Mortality in Females

In this connection the behaviour of the female rates in this country is most interesting. By both methods of analysis there has been a shift of the peak towards earlier life, and this can occur only if there has been a real change in the age-distribution of mortality. It is almost inconceivable that this could be due to a genetic influence of increasing susceptibility, or to worsening environment, despite what has been written about the habits, pastimes, and occupations of the modern young adult female, since the finding applies also to those aged 10-14. Much the most satisfactory explanation would be a transfer of primary infection from infancy and childhood to adolescence, leading to an increase in the proportion of acute disease at this age, and hence an even more sharply peaked curve of age-distribution of mortality. In the absence of direct evidence of the age at which Mantoux conversion has mainly taken place this is an extremely difficult problem. Bradford Hill (1936) accepted the mortality at ages under 5 years as a measure of the extent of childhood infection. Changes in this childhood death-rate in specific areas were found to be unrelated to changes in the mortality at early adult ages in subsequent years. He concluded that "in general the statistical evidence available (admittedly slender) does not suggest that the level of the phthisis *death-rate amongst young adults in different areas of* the country is materially due to different degrees of immunisation in childhood." He dealt solely with comparisons *between areas within the country*, and I suggest that a change affecting the country as a whole would not be readily revealed in this way.

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* The Milroy lectures for 1952, delivered before the Royal College of Physicians on Feb. 12 and 14.

Other possible causes of the arrest in decline in young adults have been advanced, notably a cessation of improvement in living conditions. Wolff (1940) suggested that the *arrest of decline in young adult females* in the United States and this country after the first world war might be due to the increase in birth-rate which occurred at that time, and that the strain of pregnancy was responsible. Considered for these two countries alone over a limited period of time, it appears a possible explanation; but it is extremely difficult to reconcile this theory with the fact that in this country the tuberculosis mortality of young adults showed its most rapid decline when the birth-rate was at its highest and increasing—between 1850 and 1880.

Hart and Wright (1939) published the most convincing evidence that the arrest of decline in the early years of the century was due to a cessation of improvement in living conditions. I shall later be referring to a number of aspects of their work, especially in the light of certain evidence that has become available since their analysis, particularly the results of the nation-wide tuberculin survey of school-children and young adults carried out during 1949-50.

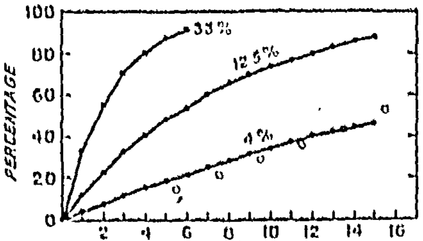


Fig. 13—Proportion tuberculin-positive at various ages for annual conversion-rates of 33%, 12.5%, and 4%. Small circles show findings in recent survey.

PRIMARY INFECTION

In this connection I wish to advance certain calculations about the relation between annual infection-rates, or conversion-rates, and the percentage positive at any given age (fig. 13). If we assume that the conversion-rate is the same at all ages, and that the position at the end of last century was that 90% of children were infected by the age of 5 years, this implies that the annual conversion-rate is 33%. If we now assume that the level of 90% infected is not reached until the *age* of 14, the annual conversion-rate would be 12%. A reduction of the annual conversion-rate from 33 to 12% merely postpones the age at which 90% of children are infected from the age of 5 years to that of 14. To reach what is probably the present level of 40% *infected at the age of* 14, the annual conversion-rate must be 3-4% if evenly spread over the first 14 years of life. The small circles in fig. 13 represent the findings of the recent survey, and indicate a conversion-rate of 5% per annum during school life. The figure of 15% at the age of 5 years suggests that the conversion-rate in early childhood is only about 3%. It seems very probable that in the last 50 years there must have been a fall in the infection-rate of this order of magnitude—i.e., from 33% to rather less than 4%—so the stage was all set for a transfer of primary infection to have begun some time in the last 50 years. There is unfortunately no further adequate evidence from tuberculin surveys to suggest at what period *the change took place.* It is possibly not a coincidence that the *tuberculosis mortality-rate* for the first 5 years of life has fallen to much the same extent—i.e., to a tenth of its original value—suggesting that practically the whole of the fall of early childhood mortality has been the result of postponement of infection from this period of life.

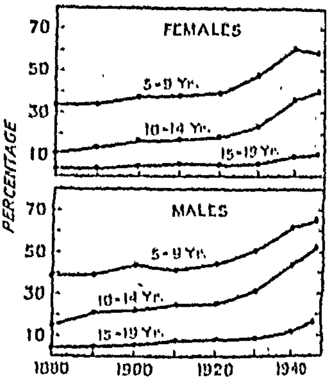


Fig. 14—Mortality from tuberculous meningitis shown as percentage of mortality from all forms of tuberculosis.

Dahl (1933) suggested an indirect method of assessing the extent to which primary infection was occurring at any age. This is based on the pathological observation that tuberculous meningitis usually occurs during the stage of dissemination shortly after primary infection, and accordingly that any increase in primary infection would be reflected in an increase in the proportion of deaths due to tub [illegible]. Hart and Wright (1939) applied a [illegible] method to young adults of England and Wales for 1913-30 and showed an *essentially negative result.* However, 1913 is well after the period of the beginning of the arrest of decline, and the rates for the next decade are liable to be affected by the war. Accordingly, I have extracted the deaths from tuberculous meningitis in *age-groups* up to age 25 years over a longer period.

The method *adopted* by Hart and Wright (1939)—i.e., expressing meningitis deaths as a proportion of all tuberculous deaths—shows that there can be no doubt that there has been a considerable increase in the proportion of meningitis deaths in older children and young adults (fig. 14); in females aged 10-14 from about 10% at the end of the last century to about 40% in recent years, and aged 15-19 from under 5% to over 10% in the same period. The changes in males have been at least as great.

If, however, we try to identify the period at which this change began on a large scale, fig. 14 seems to suggest a period in the 1920s rather than earlier, and this is some time after the decline in *young adult* mortality had slowed down.

Actually, the method suggested by Dahl (1933), depending on tuberculous meningitis, was a little different from this: he used the absolute death-rates for tuberculous meningitis and not the proportion of tuberculosis deaths due to tuberculous meningitis. Applying this to and and Wales 5) we find that in aged 5–9 years was little change 1910, since when ates have fallen ply. This reduction means, I take it, considerable bers were reaching the age of 10 years out being infected and therefore not k of tuberculous ingitis. At the f 10–14 the rates little change re 1920, since n they have fallen. At the age of 15–19 there has little change.

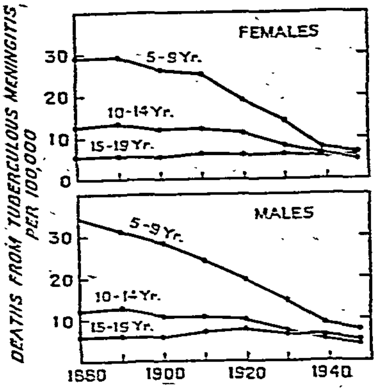
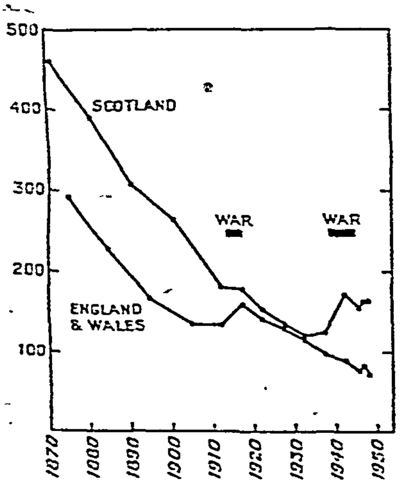


Fig. 15—Mortality-rates from tuberculous meningitis in England and Wales.

rom these two methods it seems fairly clear that there after 1920 a fall in the tuberculous meningitis death- and, at the same time, that these decreasing meningitis deaths represent an increasing proportion of all rculous deaths. This apparently paradoxical result think, not surprising when it is realised that, with ng infection-rates, two things happen so far as young lts are concerned: there is a larger pool of non- cted children leaving school, but their annual rate of ction is also becoming less. On this basis a fall- tuberculous meningitis-rate per 100,000 population cts the lowered risk of infection of the negatives, the increasing proportion of meningitis deaths to r forms of tuberculosis suggests an increasing amount lisease directly after primary infection.

hese contrasting effects were, I believe, overlooked Hart and Wright (1939) when they suggested that the mption of a decline in rates about 1935 was evidence inst the earlier arrest being due to primary infection. he risk of infection is diminishing faster than the l of negatives is increasing, there will be a decline uberculosis mortality, and, sooner or later, we would ect this stage to be reached.

rom considering recent tuberculin surveys and deaths n tuberculous meningitis I have no doubt that a siderable proportion—perhaps more than half—of tuberculous disease and deaths now seen in young adults in this country is a direct sequel of primary infection. I must admit, however that the evidence seems to point to the main transfer of primary infection to young adult life to have begun in the 1920s, and therefore too late to explain the arrest of decline of mortality which began in the early years of the century.



r. 16—Mortality from all forms of tuberculosis in females aged 15–24.

SCOTTISH AND ENGLISH EXPERIENCE COMPARED

I was not, however, entirely happy about Hart and right's explanation of the arrest of decline—namely, at it was due to an arrest in improvement of living conditions, to which young adults are assumed to be particularly susceptible. Their statistical evidence of the arrest of improvement in living conditions I cannot challenge, but there seems to be no ground for the assumption that young adults would be particularly susceptible to this, since their greater susceptibility is already allowed for in the age-distribution of mortality. In this connection I would like to compare the rates for Scotland with those for England and Wales.

If the tuberculosis mortality-rates for young adult females in Scotland are compared with those for England and Wales, we see (fig. 16) that they are constantly at a higher level with a lag of some 20–25 years behind those for England and Wales. Surprisingly, the rates for Scotland show little or no disturbance around the years of the first world war; there was an increase during the actual war years, but the rates for 1920 are greatly below those for the early 1900s, whereas in England and Wales no real improvement took place in this interval. If we consider the second world war, the position is reversed—in each country some increase during the actual war years, but this time it is England and Wales which shows the rapid recovery to levels which might have been expected with no war, whereas the rates in Scotland remain at a high level after the war. Two further points in common between Scotland in the second war and England and Wales in the first war may be noted: (1) in each case the check to the fall antedated the outbreak of war by some years (from 1905 in England and Wales, from 1930 in Scotland); (2) the absolute rates at which the arrest begins are remarkably similar, about 120–130 per 100,000. These facts prompted me to do a little juggling and to superimpose the rates for Scotland, second war, on those for England, first war, so that Scotland 1939 corresponded with England 1914, but keeping the vertical scale of mortality-rate the same for each. There is a remarkable degree of similarity (fig. 17).

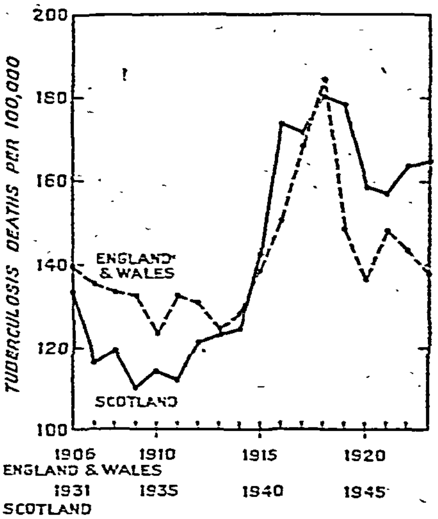


Fig. 17—Mortality from all forms of tuberculosis in females aged 15–24 in periods covering wars of 1914–18 and 1939–45.

The only conclusions I wish to draw from this are that Scotland is only now experiencing what England and Wales experienced in the 1920s; and whatever was the cause in one case is likely to be the cause in the other. Further, this cause is not likely to be some comparatively temporary factor associated with the wars. In particular, I do not accept Elliot's (1949) suggestion that the present position in Scotland is due to the large influx of Poles with particularly virulent organisms.

What I suggest is that in each case the arrest of decline is due to transfer of primary infection to young adult life. What, presumably, Hart and Wright would say is that the improvement in conditions in Scotland followed a different pattern from that in England and Wales. I have tried to explore both these possibilities. It is impossible to get a really satisfactory index of wages or living conditions separately for the two countries: I have, however, obtained some wage-rates for labourers in Edinburgh, Birmingham, and London, and comments on them by Bowley (1951). These certainly suggest that living conditions improved later in Scotland than in England and Wales, and possibly also continued to improve after there had been some arrest of improvement in England and Wales. But, by the 1930s, national wage agreements had made for a considerable degree of uniformity in these indices throughout this island; hence it seems possible for the continued fall in tuberculosis mortality in Scotland between 1900 and 1920 to be due to improving conditions at a time when there was little improvement in England and Wales.

Turning now to the question of primary infection. Tuberculin surveys show fewer negatives in young adults from Scotland, *suggesting that infection-rates there are higher.* I have repeated the calculation of tuberculous meningitis as a percentage of tuberculosis deaths for young adults of Scotland with the following results: *the percentage of deaths due to meningitis increased* a little between 1920 and 1930, and then quite sharply between 1930 and 1940, by which time it was at quite a high level. It seems from this that there was, in the late 1920s and after, some increase in the extent to which primary infection was occurring in young adults in Scotland.

AN INTERPRETATION

I wish now to put this arrest of decline in a slightly different way, suggested to me by the cohort method of analysis, and linking up with Hart and Wright's work.

The arrest is an arrest of decline of mortality in young adults in the early years of this century compared with their elders at the same time or with young adults of previous periods. Now in my discussion on cohorts one of the points I made was that the decline in mortality which began in the middle of the last century occurred first in young adults at a time when the rates for older people were not declining. If the fall began in this way with young adults, why should it not cease in the same way—young adults first? Indeed, if my further suggestion that the young adult mortality is a reflection mainly of the attack-rate of tuberculosis is correct, one would expect the arrest of decline to begin in this way.

To put it on a numerical basis, it is usual to say that the young adults of 1901–10 were doing badly because their rates fell only 12% between 1891–1900 and 1911–20, while in some older age-groups the rates were down by over 30% in this period. This overlooks the fact that in earlier years the young adult rates were falling much faster; in fact, if the young adult rates of 1901–10 are compared with those of 1851–60, the fall is 66% compared with only 50–55% in older age-groups. Indeed it is not until 1921–30 that, on this basis, there is any retardation of decline in the rates for young adults compared with older age-groups, and this period, 1921–30, is just about the time that transfer of primary infection was very likely to have become effective.

This suggestion has the further attractive feature of *bringing together under one cause the arrest of decline* in young adult females in the early years of the century and the present unsatisfactory position in older males —attributing both to a cessation of fall in the attack-rate of tuberculosis in young adults in the early years of the century, more conspicuous in young females at that time because the main part of their mortality occurs in young adult life; conspicuous in older males now because a considerable part of their mortality occurs *late in life. There is no doubt that these two apparently* separate arrests of decline in fact both occurred in people born about the same time.

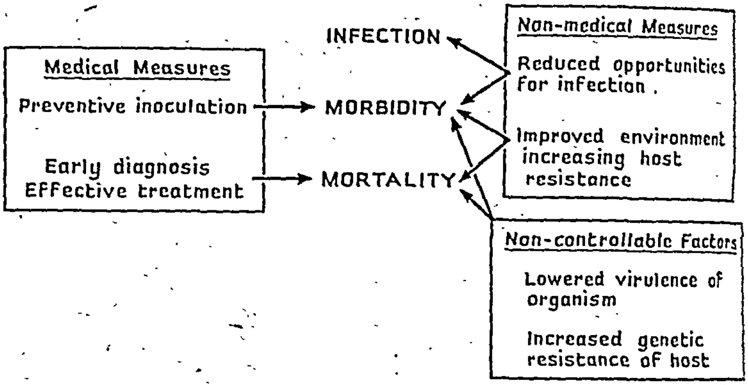

Medical Measures
Preventive inoculation
Early diagnosis
Effective treatment
INFECTION
MORBIDITY
MORTALITY
Non-medical Measures
Reduced opportunities for infection.
Improved environment increasing host resistance
Non-controllable Factors
Lowered virulence of organism
Increased genetic resistance of host

Fig. 18—Modes of action of possible causes of a fall in tuberculosis mortality.

Why is Tuberculosis Mortality Declining?

So far I have endeavoured to explain certain peculiarities of the fall in tuberculosis mortality. I would like now to consider why the rates have fallen at all. Several approaches have been made to this problem, usually by trying to show an association in time between the fall in rate and some other factor. I want now to consider the matter from a rather different angle by reviewing the various possible causes of a fall in mortality. Some of these can be decisively eliminated in the case of tuberculosis.

A reduction in tuberculosis mortality may be brought about by mechanisms operating at any of three stages: a reduction in the number of persons being infected (conversion-rate); a reduction in the number of infected persons developing disease (morbidity-rate); and a reduction in the number of patients with tuberculosis who die of the disease (case-fatality). I have distinguished between these three stages in fig. 18, and indicated at which stage various measures and factors could conceivably operate.

I have listed together medical measures which may reduce mortality—namely, preventive inoculation, which prevents the development of cases of tuberculosis in those infected, though applied to non-infected persons and, at a later stage, the early diagnosis and effective treatment of the established case. For the greater part of the period I have been discussing, neither of these can have had any appreciable influence on mortality, because they were simply not practised. Preventive inoculation has been introduced into this country only on a small scale in the last year or two. Diagnosis and effective treatment of the established case, I think it will be generally agreed, was almost non-existent before 1920, and even up to 1940 its effect on mortality was probably small, though perhaps prolonging life in individual cases. There is good reason to believe that, in the last year or two, the addition of chemotherapy to well-established collapse measures has brought about a notable fall; but there can be no doubt that, during the greater part of the period of falling rates I have been reviewing, clinical medicine in the sense of diagnosis and treatment played no great part in bringing about the fall in tuberculosis mortality.

ORGANISM AND HOST

Any change in the balance between the *infecting* organism and the infected host can affect *either the* frequency with which cases of tuberculosis *develop in* infected persons (the morbidity) or the frequency of a fatal outcome in cases of tuberculosis (the case-fatality).

First let us consider the pathogenicity of the organism. It is possible that the tubercle bacillus of today is a less virulent organism than that of a hundred years ago. However, there is no evidence for this, and I feel it should not be considered unless no other explanation is forthcoming.

Increasing natural or genetic resistance of the host erits serious consideration. I am sure that the process natural selection—i.e., the elimination by death from berculosis of susceptible persons before reproductive e—must play a big part in reducing the mortality in a pulation exposed to infection for the first time, such the Negro and the Red Indian. I would, however, pect spectacular falls in rate from this cause only in unities fairly recently exposed to infection for the st time. It seems to be generally accepted that tuberulosis has been present on a considerable scale in this untry for some centuries, and it follows that the highly sceptible strains must have been eliminated long ago. urther, as Brownlee (1920) pointed out, a fall in rate ue to natural selection is always maximal at first, and e rate of fall declines fairly rapidly as the extremely sceptible members are eliminated. Brownlee further owed that the fall in rate in this country did not follow is pattern. Within the period of recorded mortality here was at first a slow start to the fall, followed by an cceleration in decline, and subsequently a further lowing in the rate of fall. Granted the accuracy of these cts, a decline following this pattern cannot be due to a rocess of natural selection.

Dahlberg (1949) has suggested another genetic mechaism as the cause of the fall in mortality-rate, and this he erms "the break-up of isolates." By this he means a rocess accompanying the urbanisation of a previously ural community. He believes that in a predominantly gricultural community there are more or less isolated enetic groups in the various villages, and that, as these illages are amalgamated by intermarriage, genetic nfluences are at work which he expresses as follows:

> "If susceptibility to tuberculosis is conditioned by recessive enes, the break-up of isolates should cause the disease to ecome more infrequent, since the frequency of allelic genes n duplicate doses thereby decreases. Another way of xpressing the same thing is to say that the break-up of olates decreases the frequency of consanguineous marriages, nd thereby also the frequency of homozygotes.
>
> "Such a mechanism must clearly have played some part, articularly in countries with a more highly developed and xtensive industry where cities have grown at the expense of he rural population."

I am not competent to refute such a genetic influence s a cause of the fall in rate, but it does not seem to me a actor of the right type and magnitude to explain the ery considerable fall in rate which has taken place. For one thing, I doubt whether village communities in this country have ever been really isolated genetically.

LIVING CONDITIONS

By this process of elimination I am therefore led to believe that the last group of factors listed in fig. 18—i.e., non-medical measures—must be the main cause of the fall in mortality. There is no great difficulty here. The association of tuberculosis and poverty is well known and accepted, and there is no doubt that there was a great improvement in living conditions in the second half of the last century, and this has been shown by Hart and Wright (1939) to parallel the fall in mortality quite closely. Having said this and being prepared to accept environmental improvement as the major cause of the fall, I must point out just how wide a heading this is. Nutrition, housing, working conditions, and opportunities for infection, all are included, and I see little prospect of satisfactorily disentangling one of these from another.

Reduced opportunity for infection is shown separately in fig. 18, because obviously this operates mainly by a reduction in the number of persons infected, while the other environmental factors affect morbidity and fatality ates. The arrow representing superinfection as a cause of disease is put in for completeness and because I do elieve it to be a factor which cannot be ignored, though I am well aware that many of my colleagues profoundly disagree.

I want, however, to emphasise that, by the raising of living and working conditions from the bad to what may be called the moderate or indifferent, great falls in tuberculosis mortality may occur in the absence of specific medical measures, either of treatment or prevention. We should surely go on striving for the best possible environmental background and not rely solely on the potent methods of treatment now coming into our hands.

Summary

There is an underlying pattern in tuberculosis mortality associated with age: high in infancy, low in childhood, rising at puberty to reach a maximum in adult life, and with a fall in later life.

This basic pattern differs slightly in the two sexes. In infancy the male rates are higher, but this is a feature of many causes of death and is presumably not due to a factor specific for tuberculosis. During childhood there is almost no difference between the sexes, but the rise to the adult peak starts at an earlier age to reach an earlier peak in the female than in the male. In later life the male rates are the greater. The earlier and sharper rise in females is found in all communities at all times, and this suggests that it is due to some fundamental biological change associated with puberty, which is known to begin earlier in the female. There seems to be a fruitful field for research to isolate factors or influences common to both sexes at puberty but, for that very reason, operating earlier in the female. It might be found that one of these was associated with susceptibility to tuberculosis.

On this fundamental age/sex pattern a fall in the tuberculosis mortality-rate began about the middle of the 19th century. It operated predominantly in a cohort manner, probably by a fall in attack-rate of the disease in young adults, with the fall in mortality-rate at later ages occurring only as the cohort first involved became older, and a consequent shift of the age-period at which the highest rate of mortality occurred. The most likely cause of this fall was a general improvement in living conditions in the widest sense.

This improvement in mortality-rate came to an end about the end of the 19th century, and its end was similar to its beginning in that the rates for young adults were the first to show an arrest of decline, probably due to a cessation of the fall in attack-rate, in turn due to a cessation of improvement in living conditions. Older age-groups alive at the present time are still showing the results of this arrest of decline in rates, for they are the groups whose rates as young adults did not improve.

A selective arrest in the decline of mortality in young adults subsequently took place in the 1920s–1930s, because of a substantial transference of primary infection from childhood to this age-group. Only when this had progressed far enough to be counterbalanced by some passing through the young adult age-period uninfected did their rate again begin to fall about 1935.

It is too soon to analyse fully events since that time, but the gratifying fall in very recent years is almost certainly due to chemotherapy—the first time that medical effort directed specifically against tuberculosis has produced a dramatic effect on mortality-rates.

REFERENCES

Andvord, K. F. (1930) *Norsk Mag. Laegevidensk.* 91, 642.
Bowley, A. L. (1951) Personal communication.
Brownlee, J. (1918) *Spec. Rep. Ser. med. Res. Coun., Lond.* no. 18.
— (1920) *Ibid.* no. 46.
Dahl, R. H. (1933) *Acta med. scand.* 80, 323.
Dahlberg, G. (1949) *Brit. J. soc. Med.* 3, 220.
Daw, R. H. (1950) *J. Inst. Actu.* 76, 143.
Derrick, V. P. A. (1927) *Ibid*, 58, 117.
Elliot, W. (1949) *Brit. med. J.* ii, 297.
Frost, W. H. (1939) *Amer. J. Hyg.* sect. A, 30, 91.

References continued overleaf

POISONING BY BARBITURATES

SUCCESS OF CONSERVATIVE TREATMENT

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Attempted suicide by taking barbiturates is far from uncommon, and this paper is primarily a review of the treatment of 64 consecutive cases of barbiturate poisoning admitted to the wards of the medical unit of Oldchurch Hospital during the past four years.

During this period an additional 20 cases were seen in the admission unit. These patients were usually healthy adults, seen when fully conscious, who had taken a small dose of barbiturate a short while before attending hospital. Immediate gastric lavage with 2 pints of normal saline or tap-water was performed, and after observation for twelve to twenty-four hours they were discharged home. They are not included in the analysis in this paper.

Barbiturate poisoning represents about 1% of all the medical admissions to the medical unit, and in more than 80% of the cases of attempted suicide admitted alive during the four years, the taking of barbiturates was the method chosen. In all but 2 of these 64 cases the barbiturate was prescribed for the patient by his medical practitioner; and in more than 90% it was given for insomnia, either alone or as the major complaint. In a recent survey of 17,301 prescriptions on form E.C.10 (Dunlop, Henderson, and Inch 1952) barbiturates comprised 9·4% of the drugs prescribed.

The barbiturates can be divided into three groups according to the duration of their action.

1. Those which are cleared slowly by the body, requiring at least six hours for their excretion (phenobarbitone, barbitone, allobarbitone). They are excreted mainly by the kidneys, are not decomposed by the tissues, and are recoverable from the urine.

2. Those which are more rapidly excreted, usually in less than four hours (pentobarbitone, cyclobarbitone, and iso-amethyl barbituric acid are members of this group). As they are decomposed by the liver they are recovered from the urine only occasionally, and in small amounts (5–10% of iso-amethyl barbituric acid).

3. Those which are cleared rapidly are used mainly as intravenous anæsthetics, being destroyed by the body in less than one hour. They are seldom used as hypnotics (hexobarbitone and thiopentone are examples of this group).

Groups 1 and 2 are usually prescribed as hypnotics, group 2 being favoured for its rapid onset and brief action. From the point of view of a successful attempt at suicide, coma produced by group 1 (e.g., barbitone and phenobarbitone) is especially dangerous because it is more likely to be prolonged. However, the patient who has taken a group 1 drug is more likely to be conscious on admission to hospital than the patient who has taken a group 2 drug, because (possibly owing to slower absorption) the onset of stupor is delayed. One would therefore expect, other things being equal, that phenobarbitone would more often be the drug used by those admitted conscious or stuporose, and would also be more likely to cause death in the seriously poisoned. To some extent these surmises are borne out by our figures.

SEVERITY OF INTOXICATION

Although classification of cases according to severity is of value to the physician dealing with them, the criteria in every published survey differ so much that it is almost impossible to compare different series, or to compare and contrast the results of various treatments. The brief case-history given below (case X, not included in this series) shows how fallacious it is to use depth of coma and absence of reflexes, alone, as criteria of severity. Loss of consciousness to the point of coma, with absence of reflexes, certainly reflects a more serious degree of intoxication when it follows phenobarbitone or barbitone than it does when it follows pentothal or sodium iso-amethyl barbiturate. Similarly whatever the barbiturate taken, the presence of liver disease or kidney disease puts the patient into the more serious group, even if he is admitted to hospital conscious or just stuporose.

Nevertheless, we classified our cases into three groups according to their clinical condition on admission to hospital, as follows:

1. *Comatose.*—Unconscious and unrousable, diminished or absent reflexes, often subnormal temperature (cf. Chang and Tainter 1936), often cyanosed, with respiratory abnormality, and always a low or unrecordable blood-pressure.

2. *Stuporose.*—Rousable. temporarily by painful or unpleasant stimuli, occasional disorientated incoherent speech, reflexes variable, occasionally cyanosed or with respiratory abnormality, blood-pressure variable.

3. *Conscious.*—Usually able to give a rational reply to questioning (in absence of mental disorder); blood-pressure, *pulse, respiration, temperature, and* skin colour usually normal.

Although our total number of cases is small, analysis presents some interesting information.

Of the 64 cases admitted, 51 were females, and 13 males. (This ratio of 4 to 1 differs from the ratio of 2 women to 1 man recorded by Nilsson in 1951.) There were only 2 deaths, both of women. On admission 20 patients were conscious, 21 stuporose, and 23 comatose. Of the stuporose cases, 14 had been unconscious or unrousable at home, in most cases for more than twelve hours. Both the deaths were of comatose patients. Many of the stuporose group were already recovering on admission to hospital, without any specific treatment directed against the barbiturate, and this may be a pointer to suitable management of these cases. Our comatose group made up 36% of the total, whereas Nilsson's "serious" group was 50% of his total.

In most cases we were able to obtain precise information as to the nature of the drug, though we were seldom able to get precise *information* about the quantity taken.

Phenobarbitone was the drug taken in 40 cases; amylobarbitone ('Sodium amytal') in 11 cases; sodium barbitone, soluble pentobarbitone ('Nembutal'), and sodium propylmethylcarbinylallyl barbiturate ('Seconal') were responsible for 3 cases each; butobarbitone ('Soneryl') for 3 cases; and cyclohexenylethyl barbituric acid ('Phanodorm') for 2 cases. In 1 case the nature of the barbiturate was unknown, and 3 patients at least took the sodium salt of iso-amethyl barbituric acid (included above) as well as phenobarbitone, or butobarbitone or cyclohexenylethyl barbituric acid.

Phenobarbitone was taken by 17 of the 20 patients admitted conscious, 13 of the 21 admitted stuporose, and 10 of the 23 admitted comatose. Thus, if a patient attempts suicide with *phenobarbitone* there is a very

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Greenwood, M. (1927) *J. Inst. Actu.* 58, 153.
Hart, P. D'A., Wright, G. P. (1939) Tuberculosis and Social Conditions in England. London.
Hill, A. B. (1936) *J. R. statist. Soc.* 99, 247.
Lancaster, H. O. (1950) *Med. J. Aust.* i, 655.
Logan, W. P. D. (1950) *Lancet*, i, 926.
Moine, M., Oudet, P. (1947) *Bull. Inst. nat. Hyg.* 2, 211.
Picken, R. M. F. (1940) *Publ. Hlth*, 53, 145.
Springett, V. H. (1950) *J. Hyg., Camb.* 48, 361.
— (1951) *Brit. med. J.* ii, 144.
Stocks, P. (1949) *Tubercle*, 30, 50.
Wolff, G. (1940) *Amer. Rev. Tuberc.* 41, 132.

igh probability that he will not even become unconscious efore admission to hospital. Of the patients admitted omatose, 6 had taken the sodium salt of iso-amethyl arbituric acid.

The average age of the women was 40·2 years, and of he men 40·6 years. The average age of the women in he comatose group was 48·4 ± 7 years (18 patients; ange 16–71 years), in the stuporose group 38 years, and n the conscious group 32·6 ± 3·9 years (17 patients; range 21–53 years).

The youngest patient in the series was a girl of 16, admitted unconscious and known to have had asthma since infancy. The oldest patient was a woman of 71, also admitted in coma. The difference between the mean age of the comatose group and the conscious group is more than 4 times the standard error of the difference. The groups are small, and it may be that the barbiturate distribution, rather than age, was the important factor, but it does seem that the older the patients the more likely they are to develop serious toxic symptoms after taking barbiturates; and we have recently had rather dramatic experience of this.

Case X.—A man, aged 71, with severe essential hypertension was admitted with acute retention of urine. He was given sodium propylmethylcarbinylallyl barbiturate gr. 3 orally as a basal anæsthetic preparatory to prostatectomy. In 30 min. he was unconscious; after 1 hour he had areflexia, shallow to absent respiration, and cyanosis. His blood-pressure, however, did not fall. After 2–3 hours (artificial respiration was given for the first hour or so) he began to recover, and after several hours in a state resembling advanced alcoholic intoxication he recovered completely.

The age-distribution and our tentative conclusion resemble those of Heinrich (1939), and are quite unlike those of Nilsson (1951). Our figures are too small to justify division into small age-groups, but those aged 30 or under gave a ratio of 3 : 7 : 10 in the three groups of comatose, stuporose, and conscious, those aged 31–50 a ratio of 10 : 9 : 9, and those over 50 a ratio of 10 : 5 : 1. The two deaths occurred in the over-50 group. Thus, in this series nearly half our comatose group were over 50 years of age, and in the entire series of 64 patients, 16 were over 50 years of age ($p < 0{\cdot}1$ for the two groups under 50 years and over 50 years of age).

The maximal definitely known dose of phenobarbitone with recovery was gr. 100 (6·6 g.), but many patients had taken gr. 60–75 (4–5 g.) with recovery. The maximal known dose of sodium iso-amethyl barbiturate with recovery was gr. 200 (13·3 g.) and in another case was gr. 99 (6·5 g.). The dose of sodium propylmethylcarbinylallyl barbiturate taken by one of the 2 fatal cases was gr. 30 (2 g.), the dose of phenobarbitone taken by the other was not definitely known but exceeded gr. 50 (3·3 g.). The minimum dose of phenobarbitone producing coma (our most severe group) ranged from gr. 45 to 60 (3 to 4 g.). The minimal dose of sodium iso-amethyl barbiturate producing coma was apparently gr. 12 (0·8 g.). The maximum doses survived as reported by Sollmann (1942) were phenobarbitone gr. 135 (9 g.), and sodium iso-amethyl barbiturate gr. 108 (7 g.), while Nilsson (1951) reports maximum doses of phenobarbitone gr. 140 (9·5 g.) and amylobarbitone gr. 62 (4·0 g.).

Of the patients admitted to hospital unconscious, the duration of unconsciousness before admission was unknown in 9, and these all recovered consciousness within twenty-four hours. In 5 cases coma lasted twenty-four hours, in 6 cases forty-eight hours, in 2 cases three days, and in 1 case nine days; all these cases recovered. Of the 2 fatal cases (described below), one died on the day of admission after being unconscious at home for two days. The second was admitted to hospital after being unconscious for at least four days at home.

FATAL CASES

Case 1.—Age 51. This woman had advanced disseminated sclerosis, and had been bedridden for some months with dreadfully severe pain from frequent flexion spasms. The pain was only controlled by opiates in large doses or pethidine in very large doses. She had been discharged from hospital (as unlikely to benefit by neurosurgical procedure) only a week before admission here in coma. She had consumed only a small quantity of sodium propylmethylcarbinylallyl barbiturate and left a message indicating a deliberate suicidal attempt. We know that she had a supply of pethidine and promethazine; whether these drugs had been taken with the barbiturate was unknown, but considered very likely in view of her rapid death and poor condition on admission.

Case 2.—Age 56. This woman had a history of recurrent attacks of coma of unknown cause during the past fifteen years, for which she had been admitted on several occasions to other London hospitals. When admitted on this last occasion she had been unconscious at home for at least four days. Her pulse was rapid and just perceptible, and her blood-pressure just recordable (systolic 60 mm. Hg). She was cyanosed and dehydrated, with Cheyne-Stokes respiration and coarse bubbling in her lungs. Her urine was scanty, and contained a considerable amount of ketone bodies and a trace of albumin. In spite of the duration of coma, barbiturates were found in gastric washings, blood, and urine. She was almost certainly chronically addicted to barbiturates. There was no response at all to treatment. She died four days after admission. Necropsy revealed advanced bronchopneumonia and extensive active pulmonary tuberculosis.

ASSOCIATED DISORDERS

Almost every patient was interviewed by a psychiatrist before or immediately after discharge from hospital.

In all, 47 patients definitely admitted to an attempt to take their own lives, and the 2 patients who died left messages behind; thus there were 49 definite suicidal attempts among 64 patients. Of 15 patients who categorically denied any suicidal attempt, 1 had made two previous attempts and had been a certified patient in a mental hospital, and 1 had been a voluntary patient with a depressive state. 11 patients had been, or were prepared to be, voluntary patients in mental hospital, and 4 had been, or on recovery from the barbiturate were, certified insane. In 19 cases the psychiatrist expressed the opinion that the patient was suffering from a severe depressive state at the time of the attempt, and in 12 others there were severe social or domestic disturbances; 2 patients had menopausal symptoms, 6 cases had an anxiety state, 5 were epileptics, and 3 were schizophrenics. The other cases, at the time of the attempt, had among them the following organic diseases: exfoliative dermatitis (skin condition not related to the barbiturate taken), congenital hemiplegia, disseminated sclerosis, pulmonary tuberculosis, duodenal ulcer, asthma (2 cases), and severe essential hypertension; 1 was pregnant and unmarried. At least 9 of these 64 patients gave a history of one or more previous attempts at suicide.

Those patients sent home after discharge from hospital were followed up by letters sent to the medical practitioners originally responsible for their admission.

Information was obtained about 25 of them. None had made any further attempt to take his life, but 3 had been admitted to a mental hospital, 1 as a certified patient and 2 as voluntary patients since discharged; 1 patient only of these had died (of an unknown cause, in the mental hospital); 13 were apparently quite settled and happy, and no information was available about 5 who had left the district and changed their doctor. 3 were still in mental hospitals, and 1 was alive and well but had only been discharged from a mental hospital eight months before.

TREATMENT

One of us (S. L.) has had unsatisfactory experience with analeptics: patients have developed convulsive twitching of the limbs and trunk, though still unconscious. We felt, when using these drugs, that in most cases we were estimating the maximum tolerance of the human body for convulsants, rather than treating barbiturate intoxication. About four years ago, therefore, it was decided by one of us (S. L.) to abandon the use of analeptics entirely.

Since then the routine procedure has been as follows. Every patient on admission receives gastric lavage with 2 pints of normal saline or tap water in the admission unit. (In spite of the theoretical objections to this procedure in unconscious patients (Harstad et al. 1942, Nilsson 1951), and its doubtful value in late cases, we have never produced pulmonary lesions, and in a few we have removed a fair amount of barbiturate.) The patients are then sent to the medical ward, where they receive penicillin, 500,000 units six-hourly by intramuscular injection until they had been conscious for forty-eight hours, and oxygen continuously by B.L.B. mask, Tudor Edward spectacles, or double nasal catheter. At least 10 litres per minute is the rate of oxygen-flow aimed at, but this rate cannot be achieved except with the B.L.B. mask. Oxygen is continued until respiration is normal, cyanosis has permanently disappeared, and consciousness is fully restored. Pulmonary œdema, as shown by coarse pulmonary crepitations, cyanosis, and increased radiological congestive opacity, always seems to precede pulmonary infection and pyrexia, and is almost always ameliorated by oxygen at adequate concentration. There is no evidence at all that pulmonary œdema occurring in barbiturate poisoning ever responds to the administration of a 50% solution of glucose given intravenously.

Most necropsy records in barbiturate poisoning indicate the presence of bronchopneumonia (Millard 1933, Sweitzer and Laymon 1937, Marri 1939, Wile and Benson 1940), and sometimes this pneumonic process appears to be rather atypical (Sexton et al. 1941). Hence our use of penicillin as a routine. Sulphonamides are not given and we have not met with any cyanosis not attributable to a pulmonary lesion or circulatory collapse. Methæmoglobinæmia recorded by Nilsson (1951) may have been due to sulphonamides used in his cases.

No chest-thumping is practised, for it was felt that the regular nursing procedures, including turning of the patient at least every two hours, and routine care of the mouth, skin, and pressure points, is safer and more effective; nor do we feel that thumping, if it does loosen any adherent mucus in the bronchi, will encourage an unconscious patient to expectorate.

During the entire period of coma great care is taken to ensure an adequate airway by careful attention to the tongue and mouth and above all by the constant attendance of a senior (preferably qualified) nurse, until the patient was fully conscious and oriented. Laryngeal intubation, however, was not performed in any of our cases, as it was not considered necessary. We saw that they neither lost heat nor became overheated until the temperature-regulating mechanism of the body was again functioning normally. In the event of coma lasting more than twenty-four hours, fluid loss was made up by giving intravenous 5% glucose saline, 1 litre in twenty-four hours. In the absence of anuria, or severe oliguria (less than 300 ml. urine daily), precise attention to fluid balance as indicated by the blood-urea, alkali reserve (plasma-bicarbonate) and serum-sodium and serum-chloride was not considered essential unless these data showed gross variation from the normal. Continued intravenous infusion has only been considered necessary on 4 occasions; 1 of these patients eventually died. Anuria was not met in any of our cases, and severe oliguria with associated circulatory collapse only occurred preterminally in 1 of the 2 fatal cases. Catheterisation of the bladder is necessary in unconscious and some stuporose patients.

In 6 cases, in view of the possibility that a cerebral lesion might have been present, diagnostic lumbar puncture was done. This had no effect at all on the clinical condition of the patient and did not expedite recovery. Drainage by lumbar puncture was nev attempted or considered advisable. These 6 cas recovered completely.

Some of our patients were very old and some ve young; yet whatever the depth of coma they recovered, provided they were treated like any patie recovering from anæsthesia.

Though it is probable that other published seri contain occasional cases more severe than ours, w nevertheless feel that the group of patients seen this hospital must represent an adequate cross-sectio of any group of barbiturate poisoning met with in th country. It seems that with the minimum of effort an the maximum use of nursing care and common sense, should be possible to achieve nearly 100% of recoverie and that there is little need for analeptics or drast methods of treatment based on the controversial resul of animal experiment.

Since with this very simple régime deaths are rar we feel that prolonged laryngeal intubation, which ma occasionally produce fatal laryngeal œdema, is unjustifie but limited gastric lavage (which does on occasion yield large quantity of barbiturate and often a large volume stomach contents) is certainly justified. The use sympathomimetic drops to raise blood-pressure ma produce renal vasoconstriction, and interfere with th clearance by the kidney of barbiturates which hav a prolonged action.

We can see no reason why cases of barbiturate poisonin should not be treated in the ordinary general medica wards of any large hospital under the care of a consultan physician, provided the admission staff are acutely awar of the importance of immediate treatment and th dangers of delay. We should here also like to emphasis the fact that the diagnosis of barbiturate intoxicatio can be very difficult unless it is suspected in every cas of coma and stupor.

SUMMARY

We have analysed 64 consecutive cases of barbiturat poisoning treated in the wards, and 20 further case treated over the same four-year period in the admissio unit of the hospital.

There were only 2 deaths in the series.

Recovery after gr. 200 (13·3 g.) of sodium iso-amethy barbiturate is reported.

The psychiatrist's reports on these patients and some information about their eventual progress are given.

A simple régime of treatment is reported which includes neither analeptics nor laryngeal intubation.

We are grateful to the large number of doctors and nurses who during the four years have helped in the management and care of these cases. We would particularly mention Dr. P. G. Swann, Dr. J. Lister, and Dr. L. Garland-Collins. We are very grateful to Sister J. M. Turner, who has been responsible for the nursing care of most of the female patients, and to Mrs. E. D. Price for her secretarial assistance.

REFERENCES

Chang, D. K., Tainter, M. L. (1936) *J. Amer. med. Ass.* 106, 1386.
Dunlop, D. M., Henderson, T. L., Inch, R. S. (1952) *Brit. med. J.* i, 292.
Harstad, E., Moller, K. O., Simesen, M. H. (1942) *Acta med. scand.* 112, 478.
Heinrich, A. (1939) *Klin. Wschr.* 18, 1410.
Marri, R. (1939) *Sammlungen von Versiltungsfallen.* 10, 3.
Millard, R. J. (1933) *Med. J. Aust.* 2, 518.
Nilsson, E. (1951) *Acta. med. scand.* suppl. no. 253.
Sexton, D. L., Pike, G. M., Nielson, A. (1941) *J. Amer. med. Ass.* 116, 700.
Sollmann, T. (1942) Manual of Pharmacology. Philadelphia.
Sweitzer, S. E., Laymon, C. W. (1937) *Minnesota Med.* 20, 92.
Wile, U. J., Benson, J. A. (1940) *Ann. intern. Med.* 13, 1243.

"... The human mind is very like a civil servant's in-tray: Anything that does not demand immediate action is initialled and returned to Registry."—ARTHUR CALDER-MARSHALL, *The Magic of My Youth.* London, 1951, p. 135.

EMADRIN IN POSTENCEPHALITIC PARKINSONISM

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With a Note on the Pharmacology of Kemadrin by

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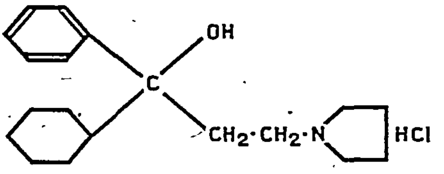
E symptomatic relief afforded by drugs of the donna group in parkinsonism has been recognised the days of Charcot (1874). Until recently the most ly used preparations were atropine, hyoscyamus, and monium, which must be pushed to the limit of rance to obtain the best results. In high doses they luce unpleasant side-effects, such as dryness of the th, paralysis of visual accommodation, drowsiness, iness, and constipation. With the introduction of newer spasmolytic drugs it was hoped that these ld be as effective as the belladonna preparations without their side-effects. The most successful them has been trihexyphenidyl ('Artane'), which introduced in 1949. 'Kemadrin' (1-cyclohexyl-1-nyl-3-pyrrolidino-propan-1-ol hydrochloride) is a



smolytic related chemically to artane and synthesised Adamson et al. (1951).

The atropine-like properties of kemadrin, its relatively toxicity, and its relationship to artane suggested a nical trial in parkinsonism. From the chronic toxicity ts it was considered safe to give to patients over g periods.

METHOD OF ASSESSMENT

Phillips et al. (1950) studied the effect of artane on 35 tients with postencephalitic parkinsonism and con- nded that it was superior to others in use at the time r the treatment of this condition. Its high cost, wever, severely limited its use in hospital practice. nce our favourable opinion of artane was confirmed by rther experience, it was decided to assess the thera- utic value of kemadrin, relatively to stramonium and tane. In our trial of artane it was found possible to ange patients abruptly from taking large doses of ramonium to artane without any of the distressing ithdrawal symptoms which occurred when less potent asmolytic drugs were substituted. The same technique f abrupt substitution was adopted in assessing the alue of kemadrin.

The trial was made on 50 patients, all of whom had dvanced postencephalitic parkinsonism and had been reated with stramonium for several years. Of these, 21 ad recently been treated with artane, and several had een given 'Lysivane' and 'Parpanit.' None received ny of the anti-histamine drugs.

Kemadrin was administered for periods varying from hree to eleven months in doses of 5–20 mg. t.i.d., the average dose being 15 mg. t.i.d. Owing to some irregularities in the supplies of kemadrin during the trial, it was necessary to substitute artane for it for periods varying from one to ten days. The two drugs were given in equal doses.

Although many objective tests have been devised for assessing the therapeutic activity of drugs in the treatment of parkinsonism (Schwab and Prichard 1951), we have not used any of them in this trial.

There is considerable variation in the patients' performance of these tests, depending as they do on suggestion, training, degree of mental concentration, interest in the task, the patient's mood, and his attitude to the investigator. For these reasons such objective tests can be most misleading. Repetition of the same test improves performance; hence, if several drugs are tested in succession, the results are likely to be better with the last drug tested than with the first. The skill with which some patients with parkinsonism play billiards has to be seen to be believed. If the patient is mentally relaxed, tremor and rigidity are minimal; if he is tense and excited, they may be severe. Emotional factors and environmental stress have a profound effect on the patient's symptoms.

The assessment of kemadrin was based on the observations of the doctors and nurses on the general appearance, activity, and mood of the patients, as well as on the opinions expressed by the patients and their relatives. Observations were made on the ability of patients to perform everyday tasks that they were either accustomed or anxious to do themselves, such as walking upstairs, dressing (including tying bows and doing up buttons), writing, and eating with knife, fork, and spoon. Great importance was attached to the observations of the nurses, many of whom have cared for the same patients for several years. The patients are so accustomed to them that emotional stress does not cloud their behaviour as it might do if they were observed by others or repeatedly subjected to tests.

To assess the effect of suggestion, 10 patients were given control tablets of lactose of the same shape and appearance as those of kemadrin for a week. Neither patients nor nurses knew that these tablets were inert.

RESULTS

Of the 29 patients treated with kemadrin who had previously been treated with stramonium, 21 were improved considerably; no improvement was noted in 6, and 2 were worse. In 21 who had been previously taking artane before treatment with kemadrin the improvement produced by artane was maintained. During the period when artane was substituted for kemadrin no change was noted in the patients. 10 patients given inert control tablets deteriorated so rapidly that at the end of a week this control trial was terminated, because we did not feel justified in continuing it.

We list below, in order of prominence, the responses that we regard as favourable:

Emotional Tone and Facial Expression.—All patients who responded favourably have shown considerable improvement in alertness and feeling of well-being. This was often reflected in the wider range of facial expression and a more cheerful countenance. Whether this improvement in emotional tone is a direct effect on the higher centres of the brain or secondary to a decrease in rigidity and muscle tone we cannot say.

Rigidity.—There was a conspicuous decrease in rigidity of the limbs and trunk, made obvious by increased freedom of movement on walking and by better posture on standing. Several patients on being questioned about the effects of the drug demonstrated spontaneously this new freedom by a movement of their arms suggesting an attempt to swim or fly. One patient (case 1) showed a particularly striking response.

Tremor.—There is a decrease in tremor, but this is not so noticeable as the reduction of rigidity. It may well be that the improvement in emotional tone is responsible for the reduced tremor, because under emotional stress tremor returns to its former intensity.

Speech.—An increase in the clarity and speed of speech noted in several patients was considered to be a reflection of the decreased rigidity and improved emotional outlook.

Vision.—The release from the greater mydriatic effect of stramonium in large doses was an advantage of great importance to many patients.

Sialorrhœa.—Freedom from dryness of the mouth produced by stramonium gave great relief to many patients. Indeed in some cases sialorrhœa became troublesome and needed correction with atropine.

Oculogyric Crises.—In spite of the claims made by some workers that artane decreases the frequency of oculogyric crises, we believe that no drug has any direct effect in controlling them. Emotional stress plays a major part in determining their occurrence at a particular time, and any improvement in emotional tone, such as produced by artane and kemadrin, will decrease their frequency, as seen in case 2.

Bowel Activity.—Stramonium in large doses leads to atony and great distension of the bowel. Volvulus of a distended large gut has occurred not infrequently in patients taking stramonium for a long time. This has not occurred in any patient taking artane or kemadrin, and the need for the relief of constipation by enemata has been reduced.

In 3 patients excessive doses of artane and kemadrin have produced giddiness. This was relieved by reduction of the dose. There has been an impression, difficult to confirm, of increased quarrelsomeness among patients taking artane and kemadrin, which may be due to their greater range of activity and facility for self-expression, and possibly to central stimulation. Case 3 stands out in this respect.

Only one patient (case 4) has complained of visual disturbance. This case is of some importance because it shows that the duration of the maximum action of kemadrin is approximately three hours. Further experience may well show that more frequent administration than used by us would be beneficial.

In no case have toxic effects necessitated withdrawal of the drug.

Tolerance, or increased dosage to maintain a given therapeutic effect, has not been observed so far.

CASE-RECORDS

Case 1.—A man, aged 39, severely afflicted with postencephalitic parkinsonism since the age of 14, had been completely incapacitated for the last two years. He had to be dressed and fed and was carried from his bed to an armchair in the morning, where he remained until the evening. On kemadrin 20 mg. t.i.d. he has improved so considerably that now he can dress and feed himself and walk about unaided, albeit with a slow and shuffling gait.

Case 2.—A man, aged 47, had moderately severe postencephalitic parkinsonism. He could fend for himself, and tremor was slight, but rigidity slowed his movements, and sialorrhœa was troublesome. Oculogyric crises occurred once or twice a month, mostly the day after his relatives had visited him, or if he had been upset by another patient or member of the staff. Kemadrin 15 mg. t.i.d. gave him considerably greater relief from rigidity than did stramonium, but there was no decrease in frequency of oculogyric crises. He was given dummy tablets for a week and immediately he became depressed, rigidity increased, and sialorrhœa became more troublesome. Concurrently oculogyric crises occurred two or three times a day. When kemadrin was given again, he immediately improved, and since then oculogyric crises have occurred only at the usual intervals.

Case 3.—A man, aged 37, had been an inmate of Highlands Hospital since 1937 with advanced postencephalitic parkinsonism. Although he could dress and feed himself and walk unaided, rigidity severely disabled him, but tremor was moderate. He improved considerably on kemadrin 10 mg. t.i.d. but became conscious of being more excitable and of feelings of aggressiveness. He requested a reduction in the dose. Improvement in rigidity was maintained on 5 mg. t.i.d., and the feelings of aggressiveness disappeared.

Case 4.—A man, aged 46, with moderate rigidity and tremor, who had previously been treated with moderate doses of stramonium, was given kemadrin 10 mg. t.i.d. He improved considerably but said that about an hour after each dose and for the consecutive two to three hours his vision was blurred on reading small print. He thought that the benefits of the treatment outweighed its disadvantages.

DISCUSSION

We have made no attempt at a detailed analysis of our results. Parkinsonism remains an incurable and terribly distressing malady and no therapy can at present do more than alleviate some of its more florid symptoms. We consider that our observations show that kemadrin can bring relief to these patients. The trial of 10 patients with inert tablets was not a true control experiment, because they had previously been taking kemadrin. However their deterioration was so immediate and unequivocal that one must conclude that kemadrin has a true therapeutic effect in parkinsonism.

Although we have been at pains to assess the relative merits of kemadrin and artane, we have not been convinced that there is any significant difference in their action. As noted above, it was found possible to change patients from one drug to the other without causing any apparent change in their clinical condition.

All our patients were postencephalitics of long standing, and we have no experience of the value of kemadrin in other forms of parkinsonism. It may be that in these conditions initial doses should be smaller than those we have used. We have found no contra-indication to the use of the drug: in particular hypertension is not a contra-indication.

We have not tried kemadrin in any patient with parkinsonism and glaucoma, but one patient with bilateral glaucoma has been taking artane for several months. He requires frequent instillation of eserine into the conjunctival sac to maintain miosis, but artane does not seem to have produced any deterioration in his eye. As kemadrin has no greater mydriatic effect than artane, it is likely that, if due care is taken, it can be used in patients with glaucoma.

Pharmacology of Kemadrin

(A. F. G.)

The pharmacological properties of artane were described by Cunningham et al. (1949); and, like that drug, kemadrin has a considerable resemblance to atropine.

Spasmolysis.—Kemadrin abolishes the responses of the isolated guineapig and rabbit ileum to acetylcholine and carbachol. On the guineapig ileum it is about one-seventh as active as atropine sulphate against muscarine and acetylcholine. Higher concentrations of kemadrin antagonise spasm due to histamine and barium. A concentration of 10^{-6} will reduce the tone and mobility of the isolated rabbit ileum. In the dog under pentobarbitone sodium intravenous injection of up to 4 mg. per kg. body-weight did not affect spontaneous bowel movement but lessened the spasm following histamine, barium, or eserine.

Mydriasis.—Kemadrin is one twenty-fifth as active as atropine sulphate as a mydriatic when tested in mice thirty minutes after intraperitoneal injection. The activity ratio of the two compounds remains the same when carbachol (0·0125 mg. per kg. body-weight) is injected intravenously as a myotic. Mydriasis is of shorter duration with kemadrin than with atropine sulphate, both in the mouse and the dog.

Salivation.—In a comparative test in which atropine sulphate and kemadrin were injected intraperitoneally thirty minutes before the injection of carbachol (0·0125 mg. per kg. body-weight), kemadrin was one twenty-fifth as active as atropine sulphate in inhibiting salivation in the mouse.

Blood-pressure.—In dogs under pentobarbitone sodium kemadrin had no effect on blood-pressure in intravenous doses less than 0·2 mg. per kg. body-weight. Larger amounts caused sharp temporary depressions, up to 60 mm. Hg with 3 mg. per kg. Elevation of blood-pressure due to antagonism of parasympathetic effects have been observed in two dogs perfused with eserine and a cat perfused with a mixture of carbachol and adrenaline. In the cat the activity of kemadrin was one-twentieth that of atropine sulphate. The depressor effect of acetylcholine was partially reduced by kemadrin 0·2–0·4 mg. per kg., and largely abolished by 2 mg. per kg.

Respiration.—The respiration of dogs under pentobarbitone sodium was not modified by kemadrin in doses of up to 1 mg.

per kg. body-weight. When, however, the bronchioles were constricted by perfusion of eserine, kemadrin had a bronchodilator action.

Nicotine Tremors.—It has been claimed that there is a correlation between the effectiveness of drugs in parkinsonism and their ability to reduce nicotine-induced tremors in rabbits (Bovet and Longo 1951). The tremors and respiratory distress caused by intravenous injection of nicotine 0·3 mg. per kg. body-weight were reduced by prior injection of kemadrin 1 mg. per kg. and largely eliminated by 5 mg. per kg. These doses were at least as effective as the same amounts of artane.

Toxicity.—In mice the LD50 of kemadrin intravenously is about 60 mg. per kg. body-weight, but subcutaneously 300 mg. per kg. was not toxic. The intravenous LD50 of atropine is of the same order, but subcutaneously in mice atropine would be more toxic. In two dogs kemadrin intraperitoneally 5 mg. per kg. caused maximal dilation of the pupil and inhibition of salivation, but had no toxic action. In three other dogs given 20 mg. per kg. the same symptoms occurred, but in addition there were violent tremors and ataxia lasting four to five hours. One animal convulsed, but pentobarbitone sodium abolished this action. Vomiting and defæcation occurred in two dogs. The behaviour of these animals was normal within twenty-four hours.

In rats tests of chronic toxicity showed that kemadrin caused only a very slight retardation of growth, and no change in the erythrocyte-count or the histological appearance of the lung, liver, spleen, and kidney, when as much as 10 mg. per kg. body-weight was given subcutaneously each day for nine weeks.

SUMMARY

Trial of 'Kemadrin,' a new spasmolytic drug, in 50 cases of postencephalitic parkinsonism has shown that it is of considerable value in relieving some of the symptoms of this disease, particularly the rigidity, depressed emotional tone, and lack of expression.

Side-effects were seen in only 3 patients.

The therapeutic effects were indistinguishable from those of artane.

Our thanks are due to Dr. G. A. Borthwick, of Highlands Hospital, for his interest and permission to publish this report; to the nurses for their coöperation; and to Messrs. Burroughs Wellcome & Co. for supplies of kemadrin.

REFERENCES

Adamson, D. W., Barrett, P. A., Wilkinson, S. (1951) *J. chem. Soc.* p. 52.
Bovet, D., Longo, V. G. (1951). *J. Pharmacol.* 102, 22.
Charcot, J. M. (1874) *Progr. méd.* 2, 147.
Cunningham, B. W., Harned, B. K., Clark, M. C., Cosgrave, R.R., Daugherty, W. S., Hine, C. H., Vessey, R. E., Yuda, N. N. (1949) *J. Pharmacol.* 96, 51.
Phillips, J., Montuschi, E., Sharkey, J. (1950) *Lancet*, i, 1131.
Schwab, R. S., Prichard, J. S. (1951) *Arch. Neurol. Psychiat.* 65, 489.

RUBBER TUBING AS A CAUSE OF INFUSION THROMBOPHLEBITIS

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THROMBOPHLEBITIS has been recognised for several years by the resident and nursing staff of the Radcliffe Infirmary as a common complication of intravenous infusion. Some have thought that it was becoming commoner, but many have attributed this to the increase in the number of infusions given, and have looked on thrombophlebitis as an inevitable sequel to giving any fluid intravenously for more than a short time.

Preliminary Survey

As a preliminary survey 80 infusions, given to patients in the general medical and surgical wards, were observed. Information was obtained about the duration of each infusion, the fluid and volume given, and the site and method used. Of these infusions 38 were complicated by thrombophlebitis, which was defined as thrombosis of more than 1 in. of the vein, together with redness and œdema of the overlying skin; simple thrombosis without inflammation was not included.

The thrombophlebitis began at the site of the infusion and spread proximally along the vein; in severe cases the vein might be affected from the wrist to the shoulder or from the ankle to mid-thigh. The inflammation spread outwards to the surrounding fascia and overlying skin, with the result that a broad band of induration could be felt in the line of the vein. Sometimes the skin of as much as a third of the circumference of the limb was red, œdematous, and hot. The limb was often so painful and tender that the patient complained more of this than of the pain following an abdominal operation. The standard treatment was to discontinue the infusion and to apply a kaolin poultice; the process then subsided, leaving a thrombosed and thickened vein.

The fluids given were blood, issued by the Regional Transfusion Centre; normal saline; 5% glucose in water; 5% glucose in normal saline; $2^1/_2$% glucose in N/4 saline; and Ringer's solution, prepared in the hospital. The crystalloid solutions were sterilised by autoclaving at a pressure of 10 lb. per sq. in. for half an hour, after a vacuum equivalent to 10 in. Hg had been drawn. All the fluids were administered through the standard giving sets assembled by the Regional Transfusion Centre.

Thrombophlebitis occurred with blood, with saline, and with glucose; it occurred whether a needle or a cannula was used; and it occurred with two blood-transfusions lasting only four hours. But—and this seemed the most important factor—the incidence increased with the duration of the infusions (table I). There was a higher incidence with the infusions of large volume than with those of small, and in the surgical wards than in the medical, which was apparently attributable to this factor.

Replies to a circular letter, sent to the pathologists of hospitals in different parts of the country, indicated that a similar incidence of this complication was being experienced elsewhere.

Among the possible causes considered were (1) bacterial infection from the fluids infused, the giving sets, or the process of setting up the infusion; (2) an irritant in the rubber tubing or the other components of the giving sets; (3) an irritant in the fluids infused; and (4) a tissue reaction to the trauma inflicted by venepuncture or cannulation.

Investigation

INFECTION

There was no evidence that infection caused any of the 81 cases of thrombophlebitis seen either during the preliminary survey or subsequently. The inflammation, however severe, never went on to suppuration, and there was no septicæmia. Moreover, many of the patients were receiving sulphonamides, penicillin, or streptomycin. If infection were a factor in this type of thrombophlebitis, it might be expected to be more frequent after a cannula had been tied into the vein than when the infusions were given by venepuncture; but, though there was no significant difference in the incidence with each, thrombophlebitis was less frequent with the few infusions given through cannulæ.

No organisms were grown from samples of eight batches of the crystalloid solutions or from four giving sets. Cultures of soil organisms autoclaved with every batch of giving sets for a fortnight were all sterile.

RUBBER TUBING

Stokes and Busman (1920) described a reaction characterised by chills, pyrexia, gastro-intestinal disturbance, headache, and lumbar pain, which followed the intravenous use of arsphenamine. They showed that it was caused by the rubber tubing through which the solution was given. Busman (1920) reported a similar reaction after blood-transfusions given through this

TABLE I—INCIDENCE OF THROMBOPHLEBITIS WITH DIFFERENT RUBBER TUBINGS

Duration (hours)	Tubing A				Tubing B		Tubing C		Tubing D	
	Preliminary survey		Control series							
	No.	Cases	No.	Cases	No.	Cases	No.	Cases	No.	Cases
0–6 ..	23	5	16	3	8	3	7	0	6	0
7–12 ..	29	12	6	3	5	0	10	1	4	0
13–24 ..	13	7	12	7	11	3	8	1	7	0
25–48 ..	12	11	7	4	4	2	7	2	7	2
49 or more	3	3	7	5	2	2	3	2	2	0
Total ..	80	38	48	22	30	10	35	6	26	2

tubing. The effect disappeared after the tubing had been in use for some time and it could be prevented by soaking new tubing in normal sodium hydroxide. Numerous substances used in the manufacture of rubber can cause dermatitis. Eczema in a physician who was hypersensitive to rubber gloves was shown by Obermayer (1933) to be caused by a substance, closely related to mustard gas, which resulted from the vulcanisation of rubber with sulphur monochloride. Like the tubing reaction, this could be prevented by treating the rubber with alkali. The inactivation of penicillin by its passage through rubber tubing has been described by Cowan (1945).

A simple extraction experiment was made to determine whether any water-soluble substances could be obtained from the rubber used in the standard giving sets. The 5 ft. of tubing from a sterile giving set was cut into short lengths, placed in a bottle containing 500 ml. of sterile physiological saline solution, and autoclaved at 10 lb. pressure for half an hour. At the end of this time the saline was turbid, had changed to an amber yellow, and gave off a strong sulphurous odour. Chemical tests indicated the presence of sulphur in this fluid, but it was not irritant when 0·1 ml. was injected intradermally. Blood was passed through another giving set and examined for sulphæmoglobin, but this was not found.

In April, 1949, three months before the preliminary survey was begun, the rubber tubing used in the assembly of the giving sets had been changed for that of another manufacturer because of its better physical properties. A stock of the tubing previously in use remained, and sets were assembled with this and with other tubings, to compare the incidence of thrombophlebitis with each. Four series of giving sets were assembled: A, with tubing from the same batch as that in use during the preliminary survey, as a control; B, with the tubing which had previously been in routine use; C, with a translucent latex tubing widely used for infusions in America (the others were of opaque red rubber); and D, which was made by the manufacturers of A, but vulcanised in a different manner after the problem under review had been discussed with them. Some giving sets were also assembled with a white translucent plastic tubing, but this split badly on autoclaving, and the attempt to use it was abandoned. All these tubings were new, and each was cleaned by the technique in routine use for new tubing:

Coils of new tubing are first placed in a bath containing a 5% sodium-carbonate solution, and this is pumped into the lumen of the tube. The soda solution is brought to the boil and kept at this temperature for twenty minutes. The coil is next transferred to a sink, one end is fitted over a tap, and water is run through, filling the sink, which is allowed to overflow. After the lumen and the external surface of the tube have thus been washed in running tap-water for not less than forty-eight hours, the coil is cut into standard lengths, and each is pulled through with a brush mounted on a long wire. These lengths are next attached in turn to a water jet, and are finally rinsed in three changes of distilled water before drying in an oven. The giving sets assembled with this tubing are sterilised by autoclaving at a pressure of 20 lb. per sq. in. for twenty minutes, after a vacuum equivalent to 20 in. Hg has been held for five minutes.

TABLE III—COMPARISON OF INCIDENCE OF THROMBOPHLEBITIS WITH EACH RUBBER TUBING (STANDARDISED FOR DURATION AND FLUID)

Rubber tubing	No. of infusions	No. of cases of thrombophlebitis		χ^2	$\frac{\text{Obs.}}{\text{Exp.}}$
		Observed	Expected		
A	118	52	37·50	5·61	1·39
B	28	8	8·88	0·09	0·90
C	32	4	11·25	4·67	0·36
D	24	2	8·37	4·85	0·24
Total	202	66	66·00	15·22	1·00

$\chi^2 = 15{\cdot}22$, $n = 3$, $P < 0{\cdot}01$

The four series of giving sets so assembled were used at random in the surgical wards. With a view to grading the cases of thrombophlebitis into degrees of severity, it was at first attempted to conduct this trial so that the observer would not know which giving set had been used when he saw the patient. This, however, was found to be impracticable, and each case was judged by the same criteria as before.

The number of cases of thrombophlebitis which occurred with each tubing is given in table I. The incidence in the control series (tubing A) is almost identical with that of the preliminary survey, and the figures for the two series, given separately in table I, have been added together in tables II–V. With this tubing the incidence increases in an almost linear relationship with the duration of the infusions, and it is likely that the incidence also varies with the fluids given. Because of these factors, to compare one tubing with another, the expected cases with each tubing (on the hypothesis that there is no difference between them) have been calculated with indirect standardisation both for duration and fluid; the small group of infusions of over forty-eight hours' duration have been excluded from this comparison because they varied widely in duration—one infusion through tubing C ran for seven days.

TABLE II—THE FLUIDS INFUSED

Rubber	Duration (hours)	Blood		Saline: Saline + blood		Glucose: G. + blood; G. + saline; G. + saline + blood		Total	
		No.	Cases	No.	Cases	No.	Cases	No.	Cases
A	0–6	19	2	17	5	3	1	39	8 (20·5%)
	7–12	12	3	16	5	7	7	35	15 (42·9%)
	13–24	3	1	10	6	12	7	25	14 (56·0%)
	25–48	1	1	6	4	12	10	19	15 (78·9%)
	Total	35	7	49	20	34	25	118	52 (44·1%)
B	0–6	3	1	5	2	..	..	8	3
	7–12	3	0	2	0	..	..	5	0
	13–24	..	..	6	1	5	2	11	3
	25–48	..	..	2	1	2	1	4	2
	Total	6	1	15	4	7	3	28	8 (28·6%)
C	0–6	2	0	5	0	..	..	7	0
	7–12	1	0	4	0	5	1	10	1
	13–24	3	0	4	1	1	0	8	1
	25–48	..	..	5	1	2	1	7	2
	Total	6	0	18	2	8	2	32	4 (12·2%)
D	0–6	1	0	5	0	..	..	6	0
	7–12	2	0	1	0	1	0	4	0
	13–24	1	0	5	0	1	0	7	0
	25–48	..	..	4	2	3	0	7	2
	Total	4	0	15	2	5	0	24	2 (8·3%)

TABLE IV—COMPARISON OF ONE RUBBER TUBING WITH ANOTHER (STANDARDISED FOR DURATION AND FLUID)

Rubber	χ^2	P
C with D	0·29	0·70–0·50
B ,, A	1·16	0·30–0·20
B ,, C	1·28	0·30–0·20
B ,, D	1·80	0·20–0·10
B ,, C + D	3·51	0·10–0·05
A ,, D	7·65	< 0·01
A ,, C	7·80	< 0·01
A ,, C + D	14·80	< 0·001

The incidence was highest with A (44%), the tubing in routine use; somewhat less with B (29%); and least with C (12%) and D (8%) (table II). The series with the last three were small, and the differences between B and the others could quite easily have arisen by chance, but the difference between B and C + D might almost be considered significant ($\chi^2 = 3·5$ for 1 degree of freedom). The incidence may have been less when B was in routine use, but it is evident that thrombophlebitis must have been a frequent complication. The incidence with both C and D is significantly less than with A. Combining the figures for C and D, 6 out of 56 infusions with these two tubings were complicated by thrombophlebitis compared with 56 out of 118 with A. When standardised for duration and fluid the difference is still more striking, χ^2 being 14·8 for 1 degree of freedom, and such a difference would only occur by chance less than once in a thousand times. If it can be assumed that the two series are equivalent in other respects, and the distribution of the site and method of the infusions (table VI) is evidence of this, then it must be concluded that the difference is due to the rubber tubing.

Both C and D are associated with a low incidence of thrombophlebitis, and it would probably require a very long series of infusions to determine whether there is any real difference between them in this respect. As regards their physical properties, however, C is superior to any of the other three, particularly in its ability to withstand repeated autoclaving without splitting where it is under tension at its attachment to other components of the giving set; and the fact that it is translucent is also a considerable advantage. It is less rigid than either A or D, and rather more care has to be taken to see that it does not become kinked during an infusion.

FLUID INFUSED

After the preliminary survey it was observed, where one fluid was used throughout, that thrombophlebitis occurred less often with blood than with saline and most often with glucose; but the series with each fluid was small, and the difference could easily have arisen by chance. In table II the two series with tubing A have been added, and the infusions of saline alone have been grouped with those of saline and blood, and the infusions of glucose with those of glucose and other fluids. In the 118 infusions given through tubing A (of 48 hours' duration or less) thrombophlebitis occurred with 7 (20%) of the 35 blood-transfusions, 20 (41%) of the 49 infusions of saline or saline and blood, and 25 (73%) of the 34 infusions in which glucose was included. This difference in incidence is, however, largely explained by the increasing duration of the infusions in this order; standardised for duration (table V) the difference is small —χ^2 is 3·15 for 2 degrees of freedom.

But, though this difference, if the fluid were all the same, could arise by chance slightly more often than once in ten such series of infusions, it is not unlikely that there is a real difference, for two reasons:

(1) It is well recognised that thrombophlebitis not uncommonly occurs after the intravenous injection of glucose in high concentration, and *it is possible that the 5% glucose may similarly cause this, especially when given by slow infusion.*

(2) The pH of the saline and of the glucose solutions is known to be sometimes as low as 4—attention has recently been drawn by Todd (1951) to the degree to which some fluids for intravenous therapy can vary from neutrality. And if the flow of blood through the vein into which the infusion is given is small or non-existent, and if the fluid infused is of this degree of acidity, it may well contribute to the onset of thrombophlebitis.

SITE AND METHOD OF INFUSION

It is a common clinical impression that the site of an *infusion and the method by which it is given are factors* in the onset of thrombophlebitis. It is said, for instance, that the onset is earlier in the lower limb than when a forearm vein is used; that the forearm veins tend to thrombose earlier than those of the antecubital fossa; and that thrombophlebitis is naturally more common after cannulation than after venepuncture. The site and the method of infusion, in so far as they are related to the flow of blood through the vein into which the infusion is given, may be factors if a sclerosing substance is being injected. However, it is not apparent, from the infusions given during the trial of the rubber tubing, that they make very much difference; or, at any rate when those in the upper limb are compared with those in the lower limb, and those by venepuncture with the few by cannulation, the differences, if any, cancel each other out (table VI).

TABLE V—COMPARISON OF INCIDENCE OF THROMBOPHLEBITIS WITH BLOOD, SALINE, AND GLUCOSE INFUSED THROUGH RUBBER TUBING A (STANDARDISED FOR DURATION)

Fluid infused		No. of infusions	No. of cases of *thrombophlebitis*		χ^2	Obs. / Exp.
			Observed	Expected		
Without glucose	Blood ..	35	7	11·51	1·77	0·61
	Saline or saline and blood ..	49	20	20·69	0·02	0·97
With glucose		34	25	19·81	1·36	1·26
Total		118	52	52·01	3·15	1·00

$\chi^2 = 3·15$, $n = 2$, P is between 0·3 and 0·2.

OTHER POSSIBLE FACTORS

Trauma inflicted with the needle may produce a simple local thrombosis; but it is impossible to explain the widespread inflammation on this basis, and the few cases of simple thrombosis have not been included.

The rubber tubing of some of the giving sets in use during the preliminary survey had probably been used before, and it was suggested that thrombophlebitis might be caused by this if it had not been effectively

TABLE VI—SITE AND METHOD OF INFUSION

—	Tubing A (control series)		Tubing B		Tubing C		Tubing D		Total		S.E.	Diff./S.E. of Diff.
	No.	Cases	No.	Cases	No.	Cases	No.	Cases	No.	Cases		
Upper limb.. ..	35	17	25	8	29	5	21	2	110	32 (*29·1%*)	±4·35	0·2
Lower limb.. ..	13	5	4	2	5	1	3	0	25	8 (*32·0%*)	±9·13	
Not recorded ..	..	..	1	0	1	0	2	0	4	0		
Needle	43	20	28	10	31	5	21	2	123	37 (*30·1%*)	± 4·09	0·8
Cannula	5	2	1	0	4	1	5	0	15	3 (*20·0%*)	±11·72	
Not recorded ..	..	..	1	0	..	..	..	..	1	0		

cleaned of all traces of blood; and it is admittedly very difficult to ensure that opaque tubing is absolutely clean. However, the incidence in the control series, in which all the rubber was new, was almost identical with that in the preliminary survey.

There is no direct evidence that the other components of the giving set (glass and metal) are not factors; but the low incidence with tubings C and D suggests that it is unlikely that they are.

At the conclusion of this investigation, as an alternative to the infusion fluids prepared in the hospital, a further five infusions were observed in which Baxter 'Vacoliter' fluids were given through tubing A instead of through Baxter tubing. Three were followed by the most severe degree of thrombophlebitis.

CONCLUSIONS

The incidence of thrombophlebitis is high; nearly half the patients who received intravenous infusions through the standard giving sets suffered this painful complication. The incidence with these sets increases in an approximately linear relationship with the duration of the infusions. This complication seems to be principally due to the rubber tubing with which these sets are assembled, since it does not occur with the same frequency when some other tubings are used. The close correlation of incidence with duration suggests that a sclerosing substance is gradually extracted from the 5 feet of tubing of the standard giving set by the fluid passing through it. This is not the only cause of this complication; probably some glucose and saline solutions can, by themselves, also cause thrombophlebitis.

By reducing the duration of the infusions the incidence will also be reduced, as Carter (1951) has shown; but with the tubings in routine use during the last few years it will not be prevented, unless the duration is limited to a very few hours; this complication occurred with the transfusion of 2 pints of blood in four hours through tubing A to one patient, and with the same volume of blood in six hours through tubing B to another.

It has been evident since the work of Stokes and Busman (1920), who were the first to recognise that rubber tubing could cause a reaction in intravenous injection, that the biological effects as well as the physical properties of rubber are of importance. It is desirable that positive standards should be determined for the constitution of rubbers which are to be used for therapeutic purposes. It is possible that some complications in the use of rubber catheters, surgical drains, and endotracheal tubes may be explained on a similar basis. Perhaps, as Stokes and Busman said in their paper, "the publication of our results may stimulate further investigation and serve, too, as a caution to those of us who are disposed to put the blame for every accident on . . . the operator's technique."

SUMMARY

Thrombophlebitis followed intravenous infusions in 38 of 80 patients seen during a preliminary survey.

In an investigation into the causes of this complication, giving sets assembled with four different rubber tubings were used for the infusion of 139 patients. Analysis of the data showed that with the tubing in routine use the incidence of thrombophlebitis increased in an approximately linear relationship with the duration of the infusions; that the thrombophlebitis was principally due to this tubing; that the incidence was very much less with two other tubings; and that some of the glucose and the saline solutions could probably, by themselves, also cause this complication.

The biological effects of rubber need further investigation, and standards should be determined for the constituents of rubber used for therapeutic purposes.

We are grateful to Dr. A. H. T. Robb-Smith, at whose suggestion this investigation was begun, for his advice and encouragement; to Dr. Ian Sutherland and Dr. W. T. Russell, of the Institute of Social Medicine, for statistical advice; to Mr. W. Trillwood, director of pharmaceutical services, United Oxford Hospitals, for many helpful suggestions, and for his observations on the pH of the saline and glucose solutions; to Mrs. E. R. Peck and Miss G. Timms for assembling the giving sets; to the resident and nursing staffs of the surgical wards, who did much of the practical work, for accepting this extra burden to their crowded days; to the surgeons, who permitted these observations on their patients; and especially to Mr. D. A. Abernethy, who first drew attention to this problem.

We should also like to record our appreciation of the interest shown by William Warne Ltd., the manufacturers of rubber tubings A and D; the Leyland & Birmingham Rubber Co. Ltd., the manufacturers of B; and John Bell & Croyden, who supplied the latex tubing C, made for Baxter by Rubber Latex Products, Cuyahoga Falls, Ohio.

REFERENCES

Busman, G. J. (1920) *J. Lab. clin. Med.* 5, 693.
Carter, J. F. B. (1951) *Lancet*, ii, 20.
Cowan, S. T. (1945) *Ibid*, i, 178.
Obermayer, M. E. (1933) *Arch. Derm. Syph.* 27, 25.
Stokes, J. H., Busman, G. T. (1920) *J. Amer. med. Ass.* 74, 1013.
Todd, R. M. (1951) *Lancet*, i, 982.

PANCREATICOGASTROSTOMY

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Wells and Annis (1949) have reported their experience of pancreaticogastrostomy in dogs. Of six dogs in which the pancreatic tail was implanted into the stomach five remained well until killed on the 15th, 45th, 49th, and 66th days. In all six dogs the implant was intact and showed no signs of leakage or inflammation. Histological section showed the success of the anastomosis in the dog killed on the 66th day. Dissatisfaction was expressed with the customary implantation of the pancreas into the jejunum in operations on man for carcinoma of the ampulla or of the head of the pancreas. It was cautiously suggested that implantation of the remaining pancreas into the stomach might offer a safer solution to a problem which troubles many surgeons.

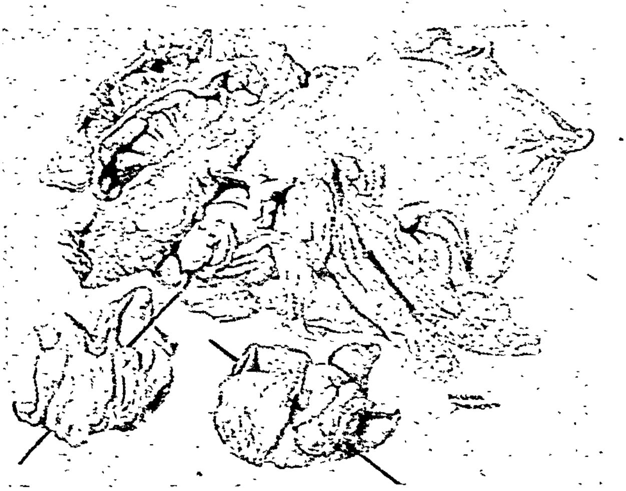
Is a technique of anastomosis available with less immediate postoperative risk than pancreaticojejunostomy? Is there a method which may permit the re-establishment of the flow of any remaining external secretion into the gastro-intestinal lumen? A mortality or morbidity rate less than that accepted for other methods of dealing with the pancreatic remnant readily answers the first question. That the reimplanted organ works as required is not so easily demonstrated. Studies of gastric content for pancreatic enzymes are not easy; indirect assessments by estimations of the fat-content of the stools are relatively vague, and, finally, gastroscopy to view secretion from an implanted duct is perhaps an optimistic procedure.

Since 1949 we have heard good reports from other surgeons and we have utilised pancreaticogastrostomy on three occasions. This experience is now recorded.

CASE-RECORDS

Case 1.—Mrs. A., aged 58, was admitted on Feb. 26, 1951, with a history of progressive loss of weight for four months, anorexia and severe jaundice for four weeks. On examination the positive findings were those of obstructive jaundice and a palpable gall-bladder.

On March 2 a pancreaticoduodenectomy was done for carcinoma of the head of the pancreas (Professor Wells); the biliary tract was reconstituted by anastomosis of the jejunum to the common duct; the jejunum was anastomosed to the divided pyloric antrum; and the cut end of the



Necropsy specimen from case 3. The smaller portions of the tissue in the lower part represent the fragment removed in different aspects. The larger specimen above shows, on the left, the loop of jejunum anastomosed to the stomach and, below towards the right, the pancreas. This has been split in its length to display the duct. The anastomosis to the stomach is clearly seen.

pancreas was implanted into the posterior wall of the stomach. This implantation was effected by approximating the stomach around the pancreas with interrupted catgut sutures.

The postoperative course was uneventful. Six months later the patient was in good health, although little weight had been gained. She reported that she passed rather bulky fatty stools.

Case 2.—Mrs. B., aged 65, was admitted on March 5, 1951, with a history of six weeks' progressive jaundice, with loss of weight for at least six months.

On March 9 a pancreaticoduodenectomy was done for a carcinoma of the head of the pancreas (Mr. Shepherd). The biliary tract was reconstituted by anastomosis of the gall-bladder to the jejunum, the jejunum was anastomosed to the divided pyloric antrum, and the cut end of the pancreas was implanted into the posterior wall of the stomach. This implantation was effected by direct suture of the cut end of the main dilated duct to the mucosa of the stomach. Interrupted catgut sutures were used, and a small rubber tube was left in the lumen of the duct, projecting into the stomach. The circumference of the cut pancreas was sutured to the serosa of the stomach.

The postoperative course was smooth, and on July 1 the rubber tube was vomited. The patient remained fairly well but emaciated. On analysis her stools showed a high proportion of unsplit fat, but meat fibres were well digested. Six months after operation she suddenly developed paraplegic symptoms and died at home. Unfortunately her death was not notified in time to arrange for a necropsy.

Case 3.—Mrs. C., aged 70, was admitted on Nov. 1, 1949, with a history of progressive jaundice for several weeks. She had lost much weight.

On Nov. 15 a pancreaticoduodenectomy was performed for carcinoma of the head of the pancreas (Mr. Gibbon). The technique used was the same as in case 1.

The immediate postoperative course was satisfactory, but on the eleventh postoperative day the patient succumbed to an acute pulmonary infection. At necropsy no peritonitis or other sign of leakage was found in relation to the three anastomoses. On dissection a free passage was demonstrated from the dilated pancreatic ducts into the stomach lumen (see figure).

DISCUSSION

Of three patients, one died from causes unrelated to the abdominal operation and two survived. The survival of these two patients and the inspection of the pancreaticogastrostomy in the third case suggests that the procedure is safe. Although the series is small, the results compare favourably with that of pancreaticojejunostomy in our recent experience.

It is difficult to be certain that the pancreatic remnant so implanted continues to secrete. The amount of its secretion may be negligible as a result of fibrotic or other irreversible changes. In fact it might be argued that, if gross dilatation of the duct is present, atrophy of the gland will be so extreme that implantation is not worth while.

In two cases the stump of the pancreas was implanted en masse with inversion of the adjacent stomach wall to maintain it in position. In the third case a dilated main duct was anastomosed to the gastric mucosa. Ferguson and Wangensteen (1950) have said that in dogs this direct type of anastomosis is most likely to succeed.

SUMMARY

Three cases of pancreaticoduodenectomy with implantation of the cut end of the pancreas into the stomach are reported: this method is thought to be safer than pancreaticojejunostomy. All the operations appeared to be technically successful.

REFERENCES

Ferguson, D. J., Wangensteen, O. H. (1950) *Ann. Surg.* 132, 1066.
Wells, C. A., Annis, D. (1949) *Lancet*, i. 97.

PANCREATICOGASTROSTOMY

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PANCREATICODUODENECTOMY for carcinoma of the head of the pancreas, the ampulla of Vater, or the associated ducts, is an established operation. The anatomical considerations (Falconer and Griffiths 1950) and technicalities of the resection have become appreciated. Reconstitution of the biliary tract by cholecystojejunostomy, or better by choledochojejunostomy, and of the alimentary tract by gastrojejunal anastomosis is accepted, but the disposal of the pancreatic duct and the neck of the pancreas remains a problem. Ligation is unsatisfactory because it either deprives the patient of pancreatic enzymes or because, if it fails, the patient is left with an internal or external fistula. Anastomosis to the jejunum is technically difficult and may also lead to a fistula. Pancreaticogastrostomy, however, has been performed successfully in dogs (Wells and Annis 1949) and the two cases reported below show that the method can be successfully applied in man.

Operative technique is simple:

The pancreatic neck with its dilated duct is mobilised for $^1/_2$–$^3/_4$ in. and two stay sutures are inserted. A small vertical incision, slightly less than the width of the pancreatic neck, is made in the posterior gastric wall. The clamp is temporarily removed from the transected stomach and the pancreatic stump is drawn through the gastric incision by the stay sutures. Interrupted sutures are inserted circumferentially from inside the stomach, uniting the pancreatic tissue to the gastric wall. No attempt is made to suture the duct, which projects into the gastric cavity; but the stay sutures are employed to anchor the pancreatic stump to the posterior gastric wall distally. Silk is probably the suture material best able to resist the proteolytic enzyme of the pancreas.

CASE-RECORDS

Case 1.—A man, aged 65, was admitted to King Edward VII Hospital, Windsor, on Feb. 28, 1951, with a history of progressive jaundice and loss of weight for six weeks. The clinical findings were those of obstructive jaundice with a palpable gall-bladder. X-ray examination showed no radio-opaque calculi.

The diagnosis of carcinoma of the head of the pancreas was confirmed at operation on March 5. Pancreaticoduodenectomy was performed. The biliary tract was reconstructed by anastomosis of the common duct and the jejunum; the jejunum was anastomosed to the divided stomach. The neck of the pancreas was implanted into the stomach as described.

The immediate postoperative condition was satisfactory, but a week later his condition deteriorated and he died on March 15.

At necropsy all the anastomoses were sound, but there was a perforation of the common duct about ½ in. from the choledochojejunostomy. This perforation, for which no cause could be found, had produced a biliary peritonitis. The pancreaticogastrostomy was satisfactory and there was no undue reaction in the stomach to its unaccustomed secretions.

Case 2.—A man, aged 65, was admitted to the Canadian Red Cross Hospital, Taplow, on Oct. 17, 1951. Three weeks before admission he had had abdominal pain, relieved by vomiting, which persisted for two weeks. Jaundice then developed and pain and vomiting ceased. The stools were clay-coloured and the urine dark, and he had lost some weight.

The gall-bladder was palpable. The direct van den Bergh reaction gave an immediate positive, and the plasma-bilirubin was 11·2 mg. per 100 ml. X-ray examination showed multiple small opacities, probably calcium carbonate stones in the gall-bladder.

Carcinoma of the head of the pancreas was found at operation on Oct. 25. There were no secondaries in the liver or elsewhere. The same operation as in case 1 was performed. Masses of calculi were removed from the gall-bladder, which was then closed.

The patient made an uneventful recovery and was discharged on Nov. 15. The jaundice faded rapidly, and two months after operation, he was symptom-free, apart from two short attacks of diarrhœa, and was putting on weight.

Pancreaticogastrostomy seems to be the most satisfactory method of dealing with the pancreatic duct in operations for carcinoma in this region, though it can, of course, have no effect on the ultimate prognosis.

REFERENCES

Falconer, C. W. A., Griffiths, E. (1950) *Brit. J. Surg.* 37, 334.
Wells, C. A., Annis, D. (1949) *Lancet*, i, 97.

VALUE OF MODIFIED STARCH AS A SUBSTITUTE FOR TALC

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OF late the evils of talc as a powder for surgical gloves have been widely discussed, and much has been published on the subject (Seelig et al. 1943, Mackey and Gil 1948, and Swingle 1948 give good bibliographie Of the several suggested substitutes praise has be given to powders prepared from modified starch (L and Lehman 1947), and a considerable pressure advertising is now brought to bear on the medic profession.

Three powders prepared from starch are sold in th country:

(1) '*K285*' (Boots).—Little has been stated other th that it is "prepared from starch which has been treated b chemical and physical means to ensure that the powde will not gel on exposure to moisture or steam sterilisation."

(2) '*Autosorb*' (Abril) is prepared from selected corn starc by the action of formaldehyde, which so modifies the starc as to prevent its forming a gel under similar conditio This substance contains a small proportion of residu formaldehyde.

(3) '*Biosorb*' (Ethicon Sutures) is described as "a mixtur of amylose and amylopectin derived from corn starch an treated by chemical and physical means to improve its lubricating value and to prevent gelatinisation when autoclaved." It contains 1% of magnesia.

TABLE I—CHEMICAL, PHYSICAL, AND BACTERIOLOGICAL TES ON TALC AND MODIFIED STARCHES

—	K 285	Autosorb	Biosorb	Talc
Microscopy, raw	As starch	As starch	As starch	Crystals
Crossed Nicol-prisms boiled	Negative	Negative	Doubly refractile	Doubly refractile
Boiled, plus iodine	Blue, lost when heated	Blue, lost when heated	Greenish	Nil
Other tests	Magneson positive Aldehyde negative	Magneson negative Aldehyde positive	Magneson positive Aldehyde negative	Magneson negative Aldehyde negative
Particle size	10·1 ± 1·4μ	11·1 ± 1·4μ	11·3 ± 1·4μ	7·6 ± 6·1μ
Lubricity	100 g.	134 g.	117 g.	125 g.
Sterility, raw	Streptothrix	Sterile	Streptothrix	Sterile

Whittet and Fairbairn (1949) describe tests applied to identify autosorb and biosorb. We have made similar tests on K285, together with an estimate of particle size made on samples before and after autoclaving for 30 minutes at 15 lb. steam pressure. A measure of lubricity was taken before and after autoclaving by measuring the weight needed to overcome limiting friction between two surfaces of membrane dusted with the powder. Suspensions of samples were examined microscopically by direct and by polarised light, and

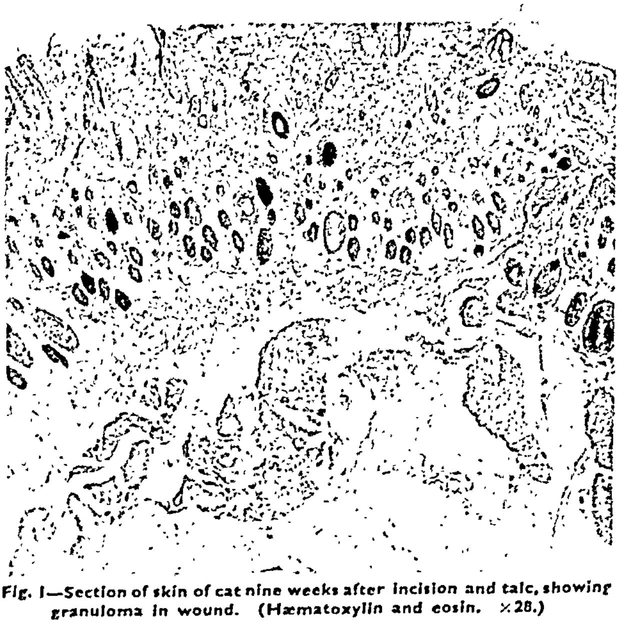


Fig. 1—Section of skin of cat nine weeks after incision and talc, showing granuloma in wound. (Hæmatoxylin and eosin. ×28.)

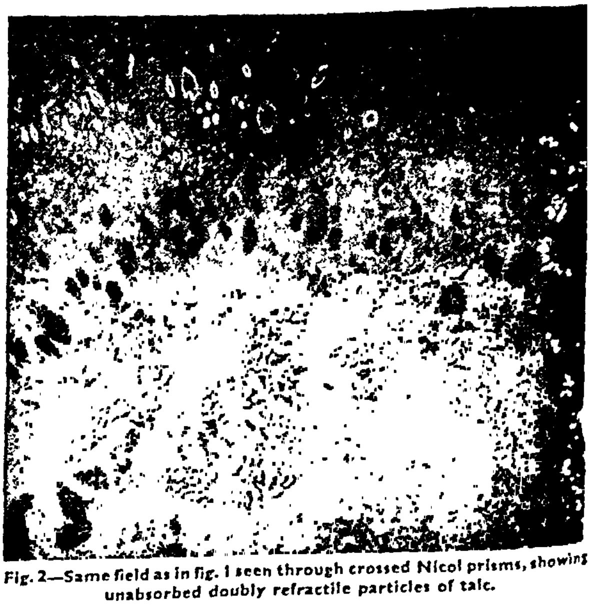
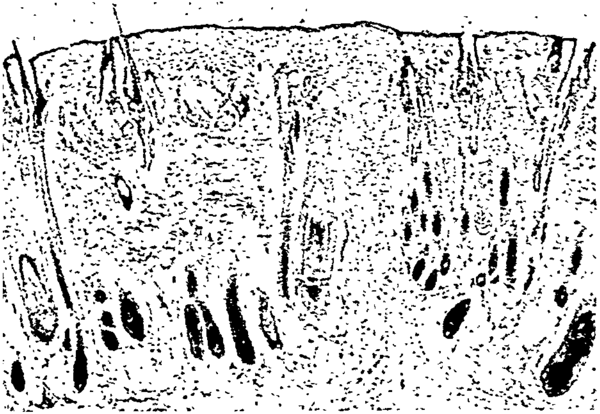


Fig. 2—Same field as in fig. 1 seen through crossed Nicol prisms, showing unabsorbed doubly refractile particles of talc.


g. 3—Section of skin of cat nine weeks after incision and autosorb, howing healing by first intention. (Hæmatoxylin and eosin. ×28.)

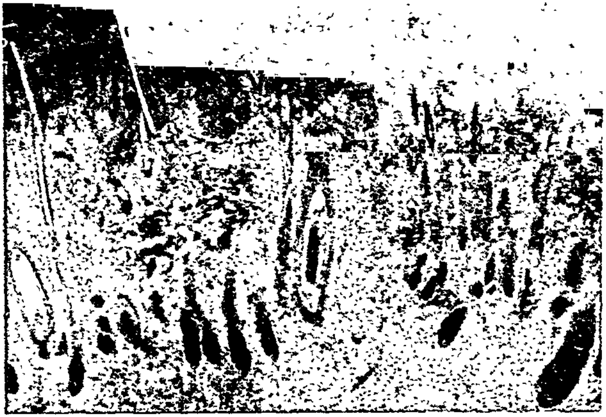


Fig. 4—Same field as in fig. 3 seen through crossed Nicol prisms, showing only hair birefringent and no particles.

cultures were made for eight weeks of samples taken before and after autoclaving.

The results are shown in table I, which shows that all three starch powders have a similar appearance and apparent origin; that they can be distinguished by appropriate chemical tests; and that the particle size s greater than that of talc, but that the granules are more regular in appearance than the crystals. After autoclaving they have a similar lubricity to that of talc, with K285 slightly superior to the others, and all three can be sterilised by routine means, though only the formalised starch can be guaranteed sterile when raw.

TABLE II—MEAN EFFECTS OF TALC AND MODIFIED STARCHES ON WOUNDS AND PERITONEAL CAVITIES

(The less damage done the smaller the score)

—	K 285	Autosorb	Biosorb	Talc	Maximum
Skin ..	4	3	2	16	20
Peritoneum	10	7·5	11	20	20

10 mg. samples of the autoclaved powders were implanted into wounds produced aseptically in the skin of the back in groups of mice, rats, guineapigs, rabbits, and kittens. A further 50 mg. was tipped dry into the peritoneal cavity through a left lateral incision. The wounds were sutured with catgut and cotton in layers. After 6–9 weeks the animals were killed and necropsies and histological examinations were made. Damage was assessed according to an empirical code ranging from 0 (no effect other than that seen in control animals with false operation) to 4 (conspicuous foreign-body reaction, granulomata, adhesions, &c., with crystals in the tissues). The results are shown in table II and typical findings in figs. 1–6, which show that the starch powders are a great improvement on talc, but are not entirely harmless, particularly in the peritoneal cavity. Talc was universally damaging; the typical granuloma containing doubly refractile particles is shown in figs. 1 and 2. By contrast the starches seem to be relatively harmless, figs. 3 and 4 showing the absence of granuloma and refractile particles in the skin after autosorb. In the peritoneal cavity the least damaging substance was the formalised starch which showed some advantage over the others. The powder containing magnesia gave rise on occasion to granulomata containing birefractile particles at a distance from the site of implantation (figs. 5 and 6).

SUMMARY

Modified starch powders advocated as substitutes for talc were examined.

Tests of physical, chemical, and biological properties indicated that, though by no means harmless, they are not inferior to talc in physical properties and are vastly superior in biological properties.

I wish to thank Prof. J. Gough and members of the Institute of Pathology, Welsh National School of Medicine, for invaluable aid in the preparation and interpretation of the microscopical sections.

REFERENCES

Lee, C. M. jun., Lehman, E. P. (1947) *Surg. Gynec. Obstet.* 84, 689.
Mackey, W. A., Gibson, J. B. (1948) *Brit. med. J.* i, 1077.
Seelig, M. G., Verda, D. J., Kidd, F. H. (1943) *J. Amer. med. Ass.* 123, 950.
Swingle, A. J. (1948) *Ann. Surg.* 128, 144.
Whittet, T. D., Fairbairn, J. W. (1949) *Pharm. J.* 109, 421.

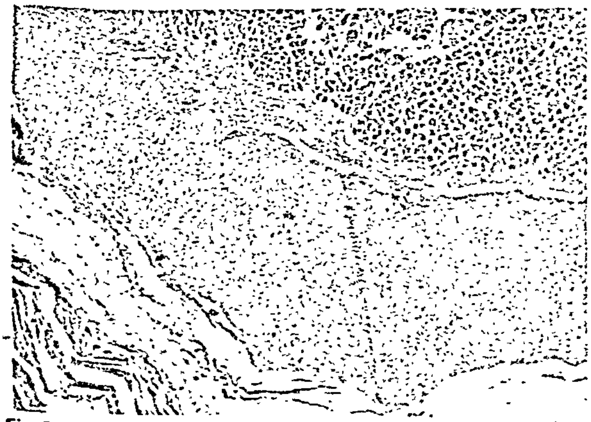


Fig. 5—Section of granulomatous adhesion between spleen and body wall of cat nine weeks after biosorb 50 mg. in peritoneal cavity, showing granuloma. (Hæmatoxylin and eosin. ×28.)

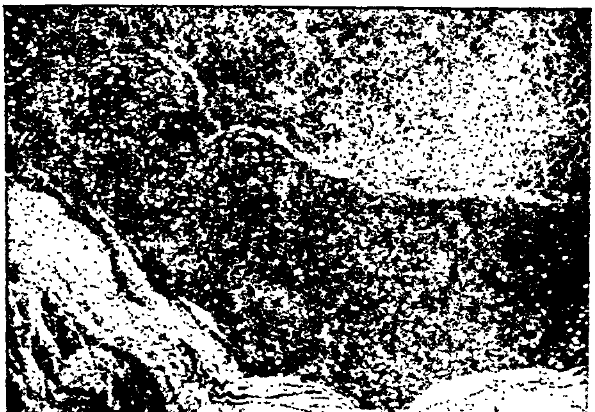


Fig. 6—Same field as in fig. 5 seen through crossed Nicol prisms, showing birefringent particles in granuloma.

SERIOUS IDIOSYNCRASY TO METHOIN

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THOUGH methoin ('Mesontoin') has only comparatively lately become available in this country, reports of its beneficial effect in epilepsy, especially grand-mal, are likely to lead to its increased use. It seems opportune, therefore, to emphasise that in sensitive persons this hydantoinate can produce sudden and disastrous toxic effects.

The Sandoz Company, of Basle, developed the drug, and Boller (1943) made the initial clinical trials in Switzerland. He advised a rather lower dosage than that since used by American workers, and he favoured a combination of methoin with phenobarbitone. He observed no clinically significant effect on the hæmopoietic system.

In the following case a very small total dose of methoin caused severe illness. I have found only one previous record of blood dyscrasia in a child treated with methoin (Ruskin 1948).

CASE-RECORD

A boy, born on July 1, 1948, was seen at the outpatient clinic on Dec. 18, 1950, with a history of eight fits in the previous fortnight. There was no family history of epilepsy or of allergy. The birth was normal, and he had thriven well in infancy. He sat up unaided at four months, walked at a year, and talked at fourteen months. In November, 1950, he had measles, with an uneventful recovery.

Physical examination, including the ocular fundi, was negative, and on his first visit phenobarbitone gr. $^1/_2$ twice daily was prescribed.

On Jan. 4, 1951, he was seen again. The fits now numbered six daily. They were of short duration but associated with falling and twitching of the face, arm, and legs. The phenobarbitone therapy was now supplemented with methoin 0·1 g. twice daily, and his mother was asked to bring him back to the outpatient clinic in a week. On Jan. 8, he became drowsy and unable to stand by himself, and these symptoms became more conspicuous each day. He became very restless at night and unable to hold a cup because of tremor. On Jan. 10, the sixth day after starting methoin, he developed a rash, and on Jan. 11 he reported at hospital. He was admitted and the methoin was stopped.

Condition on Admission

He was drowsy, disoriented, restless, uncoöperative, and pyrexial. There was an intense generalised itchy morbilliform rash on the trunk, face, and limbs, confluent on the forearms and legs. A coarse generalised tremor was accentuated by attempts at voluntary movement. The tendon reflexes were brisk, and the plantar responses flexor. The ocular fundi were normal. The throat was acutely hyperæmic and swollen, and there was a profuse purulent left otorrhœa. Examination of the blood showed Hb 12·6 g. per 100 ml.; red cells 4,620,000 per c.mm.; and white cells 4000 per c.mm. (polymorphs 56%, lymphocytes 38%, monocytes 6%).

Treatment and Progress

He was treated with intramuscular penicillin 50,000 units six-hourly. As he was not having any fits, phenobarbitone was discontinued forty-eight hours after his admission to hospital, by which time the rash had disappeared. By Jan. 18, his temperature was normal, his otorrhœa had ceased, he was much less drowsy, and his tremor had disappeared. He was allowed up and could walk with support but was much shaken by his illness. On Jan. 23, the twelfth day in hospital, he looked perfectly well, and penicillin treatment was stopped.

Within eight hours of stopping penicillin his rectal temperature was 104°F, and next day (Jan. 24) the tremor returned and his throat was intensely inflamed though not ulcerated. On Jan. 25 a white-cell count was 1800 per c.mm., and no polymorphs were seen in the blood films. He was treated with intramuscular penicillin 250,000 units six-hourly and pyridoxine 200 mg. thrice daily by mouth. On Jan. 28, the white-cell count had fallen to 1400 per c.mm., and still no polymorphs were seen in films. His gums were much hypertrophied, and he developed diarrhœa. From Jan. 29 to Feb. 1 his urine contained albumin, much bile pigment, and urobilinogen, but neither skin nor conjunctivæ became jaundiced.

By Feb. 2 he was afebrile again and improving. His diarrhœa had ceased, his urine was normal, and his tremor was subsiding. The white-cell count had risen to 24,800 per c.mm. (mature polymorphs 35%). Within another three weeks the hypertrophy of his gums had disappeared, he could walk unaided, he was free from fits, and he was allowed to return home. Throughout his illness there was no material change in the red-cell count. The changes in his white-cell count were as follows:

Date	*White cells per c.mm.*	*Mature polymorphs %*	*Immature cells %*
Jan. 12, 1951 ..	4000 ..	56 ..	0
,, 25, ,, ..	1800 ..	0 ..	0
,, 26, ,, ..	2000 ..	0 ..	0
,, 27, ,, ..	1800 ..	0 ..	0
,, 28, ,, ..	1400 ..	0 ..	0
,, 29, ,, ..	4200 ..	3 ..	26
,, 30, ,, ..	12,200 ..	4 ..	60
,, 31, ,, ..	35,400 ..	21 ..	47
Feb. 2, ,, ..	24,800 ..	35 ..	35
,, 3, ,, ..	22,200 ..	63 ..	7
,, 4, ,, ..	19,800 ..	58 ..	5
,, 6, ,, ..	14,400 ..	60 ..	3
,, 10, ,, ..	7800	50 ..	0

Follow-up

His general health has remained good, but in spite of treatment with phenobarbitone and sodium borate he is again having three to five short convulsions each day.

DISCUSSION

There is general agreement that methoin is useful for epileptics who cannot be treated effectively with barbiturates or with phenytoin (Kozol 1946, Lennox 1946, Loscalzo 1945, 1947, Ruskin 1948, Garvin and Gibbs 1950).

The early and comprehensive studies of Loscalzo (1947) and of Kozol (1946) indicated that the toxic effects were relatively mild and infrequent. Tremor, drowsiness, morbilliform rashes, prurigo, hypertrophy of the gums, and fever were reported, but they seldom necessitated the abandonment of treatment. Since then, however, serious toxic reactions have been encountered. Agranulocytosis has been reported in 5 cases (Ruskin 1948, Greenhouse and Lehr 1950, Bercel et al. 1950, Jones 1951). In these cases the white cells alone were affected, and though the patients were very ill they all recovered.

Pancytopenia has been a more usual finding; there are reports of 12 cases (Harrison et al. 1946, Bloom et al. 1948, Frank and Holland 1948, Aird 1948, England and McEachern 1949, Weller and Metcalfe 1949, Forster and Frankel 1949, Davies et al. 1950, Garvin and Gibbs 1950, Jones 1951). In 5 of these, hæmorrhagic incidents were prominent, and 1 patient became jaundiced. There was agranulocytosis and severe anæmia, and in all cases in which the bone-marrow was examined it was hypoplastic. Of the 12 patients, 7 died.

In this country the only serious abnormalities of the blood reported after treatment with methoin were those described by Jones (1951).

> Of 41 patients treated with methoin, 3 had severe reactions. One had progressive leucopenia, which cleared when methoin was withheld; another had a petechial rash and lymphocytosis, followed by recovery when methoin was withheld. The third patient, a woman aged 40, was having 0·6 g. daily with good effect when, in the eighth month of treatment, she suddenly developed ulceration of the mouth and agranulocytosis. The white-cell count fell to 700 per c.mm., with no polymorphs, and the agranulocytosis persisted in spite of treatment with penicillin, aureomycin, and blood-transfusions. The bone-marrow was aplastic, and she died from subarachnoid hæmorrhage.

The present case of idiosyncrasy to methoin is the second to be reported in a child, and I have been unable to find any previous record of serious illness following so small a dose of methoin. The boy developed symptoms after taking only 0·6 g., and the methoin was discontinued after a total dose of 1·4 g. had been given in seven days.

Abbott and Schwab (1950), reviewing the toxic effects attributed to methoin and related drugs, suggest that all cases of blood dyscrasia develop gradually through three stages :

(1) Modified normal response in which the total white-cell count is normal but stained films show a fall in the proportion of neutrophils and monocytes and a rise in the proportion of ymphocytes and eosinophils.

(2) Controlled neutropenia in which the white-cell count is ess than 3000 per c.mm. but there are no clinical abnormalities.

(3) "Runaway pancytopenia" with disastrous clinical signs.

They say that stage 1 is common, that stage 2 occurs in about 20% of patients, and that stage 3 occurs in 1% or 2% but is largely preventable if the earlier stages are recognised.

In most of the published cases of methoin toxicity, the drug was given continuously for several months before harm was evident ; but it is now apparent that in sensitive persons severe reactions can develop after a very small dose and in a very short time. Plainly, routine blood examination cannot provide evidence on which these reactions can be prevented ; and, if the use of methoin is contemplated, the following measures should be adopted to ensure that their incidence is minimal :

(1) Patients with a history of infantile eczema or other allergic diseases or of unexplained eruptions should be admitted to hospital and kept under observation for the first few weeks' treatment.

(2) Methoin should not be used until other drugs with less serious toxic effects have proved inadequate after thorough trial.

(3) Methoin should not be given in combination with other treatment known to depress erythropoiesis—e.g., X-ray therapy and troxidone.

(4) The initial dose of methoin should be very small and should be increased very gradually.

(5) The patient, or a responsible relation, should be warned to stop the methoin and report at once to his doctor if any rash, tremor, sore throat, fever, or other symptom develops.

(6) The blood should be examined at once if a patient taking methoin becomes pyrexial or unwell.

(7) If blood dyscrasia is discovered, treatment with antibiotics and hæmatinics should be started in full dosage at once, and continued for two weeks after all toxic signs have disappeared.

(8) Total white-cell counts and differential counts should be made before starting treatment and at intervals therafter.

SUMMARY

A case of agranulocytosis is described in a boy, aged 2 years, after seven days' treatment with methoin 0·1 g. twice daily. Blood dyscrasia is the only serious toxic effect so far attributed to this drug ; 17 such cases, of which 7 were fatal, have previously been published. The case presented here is the second to be described fully in this country, and the second to be described in a child.

Attention is drawn to the potential toxicity of methoin, and measures are proposed to limit the dangers of methoin treatment.

I have to thank Dr. J. H. Hutchison for permission to use the records of this patient, who was treated in his wards at the Royal Hospital for Sick Children, Glasgow ; and Prof. Stanley Graham and Dr. Hutchison for advice on preparing this article.

REFERENCES

Abbott, J. A., Schwab, R. S. (1950) *New Engl. J. Med.* **242**, 943.
Aird, R. B. (1948) *Calif. Med.* **68**, 141.
Bereel, N. A., Finesilver, B., Solomon, P., Somerfeld-Ziskind, E., Ziskind, E. (1950) *J. Amer. med. Ass.* **143**, 1460.
Bloom, N., Lynch, J. P., Brick, H. (1948) *Ibid*, **138**, 498.
Boller, W. (1943) *Schweiz. med. Wschr.* **73**, 699.
Davies, R. R., Fisch, C., Tischer, E. P. (1950) *New Engl. J. Med.* **242**, 863.
England, N. J., McEachern, D. (1949) *Canad. med. Ass. J.* **60**, 173.
Forster, F. M., Frankel, K. (1949) *Dis. nerv. Syst.* **10**, 108.
Frank, C. W., Holland, J. F. (1948) *J. Amer. med. Ass.* **138**, 1148.

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PHYSIOLOGICAL ACTIVITY OF 3:5:3'-L-TRIIODOTHYRONINE

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THE synthesis of 3:5:3'-L-triiodothyronine and its identification in human plasma has recently been reported by Gross and Pitt-Rivers (1952), and the formation of the same compound during the iodination of 3:5-diiodothyronine has been described by Roche et al. (1952). This paper describes the biological assay of this compound by its effect in preventing goitre in animals treated with thiouracil.

METHODS

Male hooded rats weighing 80–120 g. were used. All the animals had 0·1% thiouracil in their drinking-water from the first day of the experiment and were injected subcutaneously each day with either the control solution A (solvent) or the test compounds. Each group contained 10 rats with 2 rats to each cage, and the rats of higher or lower weights were distributed as evenly throughout the groups as possible ; the test lasted 10 days, and on the 11th day the rats were killed with chloroform and weighed ; the thyroid glands were removed and weighed immediately, and the weight of gland per 100 g. body-weight was calculated (Cortell 1949).

Experiment 1.—Group A (controls) received daily injections of 0·1 ml. of 0·8% saline containing 0·00025*N* NaOH ; group B received daily injections of 2 µg. L-thyroxine in 0·1 ml. of solvent A ; group C received daily injections of 2·4 µg. L-triiodothyronine in 0·1 ml. of the same alkaline saline solution. The results are given in table I.

TABLE I—RESULTS OF EXPERIMENT 1

Animal no.	Group A		Group B		Group C	
	Body-weight (g.)	Thyroid weight (mg.)	Body-weight (g.)	Thyroid weight (mg.)	Body-weight (g.)	Thyroid weight (mg.)
1	102·5	21·9	133·5	26·3	110·0	7·2
2	99·15	17·7	117·8	17·2	162·0	10·2
3	117·9	31·1	171·3	31·2	94·9	8·0
4	113·5	21·3	122·0	24·8	105·8	7·7
5	162·2	33·3	107·1	18·7	135·4	8·5
6	95·4	30·2	88·6	15·4	111·6	8·5
7	163·4	34·2	151·6	30·7	136·0	10·0
8	110·5	24·7	146·2	23·6	93·2	7·0
9	101·5	23·1	130·6	25·8	87·3	8·9
10	119·4	22·7	100·6	14·9	102·9	9·1

Experiment 2.—Group A animals were treated as in experiment 1 ; group B received 2·3 µg. L-thyroxine daily ; group C received 2·0 µg. L-triiodothyronine hydrochloride daily (an equimolecular dose to the thyroxine) ; group D received 0·5 µg. of L-triiodothyronine hydrochloride daily, all doses being administered in 0·1 ml. of solvent A. The results are shown in table II.

DR MACARTHUR : REFERENCES—*continued*

Garvin, J. S., Gibbs, F. A. (1950) *Dis. nerv. Syst.* **11**, 48.
Greenhouse, J. M., Lehr, E. (1950) *Illinois med. J.* **98**, 18.
Harrison, F. F., Johnson, R. D., Ayer, D. (1946) *J. Amer. med. Ass.* **132**, 11.
Jones, D. P. (1951) *Brit. med. J.* i, 61.
Kozol, H. L. (1946) *Amer. J. Psychiat.* **103**, 154.
Lennox, W. G. (1946) *J. Pediat.* **29**, 356.
Loscalzo, A. E. (1945) *J. nerv. ment. Dis.* **101**, 537.
— (1947) *J. Amer. med. Ass.* **135**, 496.
Ruskin, D. B. (1948) *Ibid.* **137**, 1031.
Weller, R. W., Metcalfe, J. (1949) *New Engl. J. Med.* **241**, 17.

DISCUSSION

There is a significant difference (t on 17 degrees of freedom is 3·06—i.e., P = 0·001–0·1) between the thyroid weights (expressed as a fraction of the body-weights) of the rats given equimolecular doses of L-thyroxine and L-triiodothyronine (experiment 2). The difference between the thyroid weights (expressed as a fraction of the body-weights) in the animals receiving thyroxine and 0·25 equivalent of triiodothyronine is not significant (t on 18 degrees of freedom is 0·63—i.e., P = 0·5–0·6). It is estimated from these experimental findings that the potency of L-triiodothyronine is 3–4 times that of L-thyroxine in the goitre prevention assay.

TABLE II—RESULTS OF EXPERIMENT 2

Animal no.	Group A		Group B		Group C		Group D	
	Body-weight (g.)	Thyroid weight (mg.)	Body-weight (g.)	Thyroid weight (mg.)	Body-weight (g.)	Thyroid weight (g.)	Body-weight (g.)	Thyroid weight (mg.)
1	123·0	29·7	94·7	7·7	129·2	8·2	108·5	13·3
2	151·5	42·6	132·1	15·1	123·0	8·9	105·8	8·2
3	147·3	31·1	169·1	21·1	131·0	9·0	127·2	14·6
4	148·2	33·2	134·1	7·8	157·7	10·7	104·8	10·8
5	132·4	20·4	126·8	11·1	130·7	9·3	100·0	10·1
6	111·2	28·4	183·9	24·6	116·0	12·3	119·7	8·5
7	142·6	29·2	128·6	13·2	123·8	8·8	132·8	24·1
8	160·0	29·9	170·0	20·6	133·0	11·1	108·2	12·8
9	94·7	18·7	121·2	11·8	112·5	7·3	113·2	8·2
10	120·0	21·7	113·3	10·2	1 dead		122·8	15·9

These results suggest that the formation of triiodothyronine from thyroxine may be yet a further step in the biological synthesis of the thyroid hormone as described by Harington (1944). The stages at present assumed are:

(1) Oxidation of iodide to iodine.
(2) Iodination of tyrosine to diiodotyrosine.
(3) Coupling of 2 molecules of diiodotyrosine to give 1 molecule of thyroxine.

We now have to consider the possibility of:

(4) Deiodination of thyroxine to give triiodothyronine.

Roche et al. (1951) have shown that sheep thyroid slices can deiodinate I^{131}-labelled diiodotyrosine to give monoiodotyrosine, and have postulated a dehalogenating enzyme in the thyroid gland. It may well be that this or a similar enzyme plays an essential rôle in thyroid hormone synthesis by effecting the deiodination of thyroxine to triiodothyronine. There is, moreover, evidence that such an enzyme occurs in other parts of the body; Gross and Leblond (1951) found that in thyroidectomised mice the administration of thyroxine labelled with I^{131} led to the appearance in the plasma of their compound, unknown 1, now identified (Gross and Pitt-Rivers 1952) as triiodothyronine.

At present, it is not possible to do more than speculate on the rôle of triiodothyronine in thyroid function, but the possibility clearly exists that it is the form of the thyroid hormone that is active in the tissues. Further experiments on the activity of triiodothyronine in the whole animal and also in isolated tissues are being carried out.

SUMMARY

3:5:3′-L-triiodothyronine has been assayed in rats by its effect in preventing goitre in thiouracil-treated rats. In this test its activity is about three times that of L-thyroxine.

We wish to thank Dr. W. L. M. Perry for help in the calculations of the results.

References at foot of next column

STRANGULATED FEMORAL HERNIA IN YOUNG BOY

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UNCOMPLICATED femoral hernia is uncommon children under 10 years of age, occurring once in abo every 250 cases of all types of hernia in this age-grou (Stiles 1904, Rutherford 1927, Herzfeld 1938). Thre quarters of these children were girls. Strangulation a femoral hernia in a child appears to be very ra and I have found only three other published cas (Biasini 1936, Shepler and Smith 1940, Innocenti 1946).

A boy, aged 3 years 9 months, was admitted to the W Middlesex Hospital on Oct. 28, 1950, under the care of Mr. Jo Scholefield. He had been quite well until he awoke ear that day with abdominal discomfort and pain in the rig groin. A swelling was noticed in this region by the pare for the first time. There was no vomiting.

On examination the child did not appear ill. Temperatu 99·2°F, pulse-rate 128. The tongue was moist and clea The abdomen was soft and not distended; bowel sounds we present and of normal quality. In the right groin there w *a firm tender swelling, about 1 in. in diameter, below a* lateral to the pubic tubercle; it did not transmit a cou impulse. The overlying skin was not reddened, and evidence of recent infection was found in the right low limb, perineum, scrotum, or back.

Operation was carried out the same afternoon under gener anæsthesia. Through an incision below and parallel to t right inguinal ligament the swelling was explored and fou to be a femoral sac containing bloodstained fluid and a portio of strangulated omentum. It proved impossible to retu this into the abdomen through the neck of the sac, whic was very narrow, and it was therefore ligated and excise The sac was freed from below and removed after ligation, b no repair was attempted.

The boy made an uninterrupted recovery and was discharge home on the 8th postoperative day.

The problem of diagnosis is well illustrated by th case. The family doctor had sent the boy to hospit as a case of inguinal lymphadenitis, but the admittin medical officer thought he had an irreducible right inguin hernia. The lump was in the position of a femoral hernia but, in view of the rarity of this condition in childhoo lymphadenitis seemed to be the most likely diagnosi Because of the absence of a primary focus of infectio and the nearly normal temperature with a raised puls rate it was thought wise to operate. Biasini's (193 patient, a girl of 6 had a raised temperature and wa treated for some time with poultices before operatio Inguinal adenitis is fairly common in children withou any obvious source of infection; in adults it is notoriousl difficult to distinguish from strangulated femoral herni and may be tuberculous in origin. The importance o avoiding the conservative treatment of strangulate femoral hernia under the mistaken diagnosis of inguina adenitis needs no emphasis.

Two other conditions which should be easy to exclud are femoral ectopia of a maldescended testis and psoas abscess.

I am grateful to Mr. Scholefield for permission to publish this case.

REFERENCES

Biasini, A. (1936) *Rif. med.* 52, 1618.
Herzfeld, G. (1938) *Amer. J. Surg.* 39, 422.
Innocenti, M. (1946) *Policlinico, sez. prat.* 53, 892.
Rutherford, R. (1927) *Lancet*, ii, 498.
Shepler, N. B., Smith, C. W. (1940) *Amer. J. Surg.* 49, 375.
Stiles, H. (1904) *Brit. med. J.* ii, 812.

DR. GROSS, MRS. PITT-RIVERS: REFERENCES

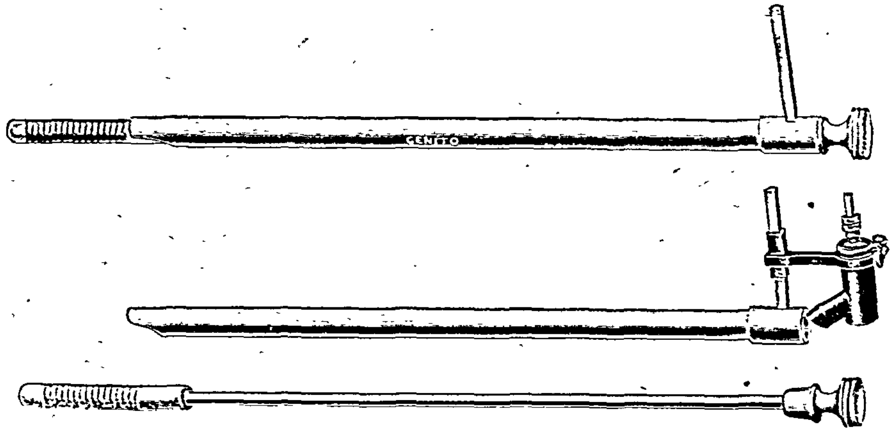
Cortell, R. E. (1949) *J. clin. Endocrinol.* 9, 955.
Gross, J., Leblond, C. P. (1951) *Proc. Soc. exp. Biol., N.Y.* 76, 686.
— Pitt-Rivers, R. (1952) *Lancet*, i, 439.
Harington, C. R. (1944) *Proc. roy. Soc.* B, 132, 223.
Roche, J., Lissitzky, S., Michel, R. (1952) *C.R. Acad. Sci., Paris*, 234, 997.
— Michel, R., Lissitzky, S., Michel, O. (1951) *Ibid*, 232, 2148.

New Inventions

FLEXIBLE ŒSOPHAGOSCOPE

THE instrument illustrated here is a rigid œsophagoscope which carries a flexible introducer. It has proximal ghting, and it is important that the light is properly ocused before the instrument is passed. The instrument s made in three lengths; for lesions of the cardia the 45 cm. tube (over-all length 50 cm.) is required. A long biopsy forcep is made for use with it.

It passes with the same ease as the flexible gastroscope. When the end of the rigid instrument is in the thoracic œsophagus the introducer is withdrawn, and œsophagoscopy is carried out in the usual way. This instrument may be passed on the conscious patient lying on his side, as in gastroscopy; or on the anæsthetised patient lying on the back. I have preferred to work with the patient under general anæsthesia with tracheal intubation.



Some may argue that to pass an instrument blindly in this way is unwise: but this instrument is designed for use in cases of mid-œsophageal or lower œsophageal lesions and only after radiological examination with a barium swallow. Under these circumstances the method is not only safe but a good deal safer than the rigid instrument in inexperienced hands.

The instrument has been made for me by the Genito-Urinary Manufacturing Company Ltd., 28A, Devonshire Street, London, W.1.

HAROLD BURGE
M.B.E., M.B. Lond., F.R.C.S.

Reviews of Books

La maladie infectieuse

V. DE LAVERGNE, professeur à la Faculté de Médecine de Nancy. Paris: Masson. 1951. Pp. 368. Fr. 2200.

CHEMOTHERAPY has transformed the treatment of many communicable diseases, but if it is to be applied to the best advantage there must be close liaison and understanding between laboratory worker and clinician. Both will find interest and value in Professor de Lavergne's clear and vivid account of bacteriology and virology. The book is a mine of information on the general biology of bacteria and viruses and the mechanisms of the various parasite-host reactions, and Professor de Lavergne also discusses such vexed topics as the incubation period, symptomless infections, tropisms, and metastases. In a final section on practice he describes laboratory diagnostic aids, treatment, especially with antibiotics—among which he gives reason for including the sulphonamides—and methods of specific prophylaxis. The text is rich in allusions to past and present bacteriologists from Pasteur to Fleming and his contemporaries, but most of the references are to recent French work.

Peptic Ulcer

Editor: DAVID J. SANDWEISS, M.D., F.A.C.P., professor of human development, University of Chicago. Philadelphia and London: W. B. Saunders. 1951. Pp. 790. 75s.

CLOSE upon the heels of Ivy, Grossman, and Bachrach's major work on peptic ulcer, another important book with the same title now appears, edited by D. J. Sandweiss. This is a compilation of the views of 77 authors selected by the American Gastro-Enterological Association and sponsored by an editorial committee of a dozen distinguished American specialists in this field—Aaron, Bockus, Daniels, Eusterman, Ferguson, Ivy, Jordan, Lahey, Palmer, Shay, Snell, and Wilbur. The numerous contributors were invited individually, but it seems that their manuscripts were reviewed by the committee and by a number of other authorities also. The finished work must thus be fairly taken to represent the authoritative teaching of the American school.

All aspects of the subject are fully covered in the book's eight sections, even to the inclusion of experimental and therapeutic trials of A.C.T.H. and cortisone in peptic ulceration—a form of treatment which has proved almost wholly disappointing. In contrast, Dr. Snell concludes that statistics of the last ten years indicate that partial gastrectomy for ulcer deserves the high popular standing which it now enjoys. Vagotomy, however, as an operation by itself is found by Dr. Jordan to be rapidly and rightly waning in popularity, and, even when combined with other operations such as gastro-enterostomy, to be less successful than gastric resection alone. About half of the book is devoted to treatment, and less than a sixth to pathogenesis and ætiology; not much space is given to environmental, occupational, and sociological factors, but a full and careful study of experimental ulcer is included. Prof. G. W. Pickering, who seems to be the only Englishman contributing to this symposium, has written a masterly chapter on ulcer pain; all the other authors, except Selye of Montreal, are actively at work in the United States.

The Hand in Psychological Diagnosis

CHARLOTTE WOLFF, fellow of the British Psychological Society. London: Methuen. 1951. Pp. 218. 32s. 6d.

IN this further book on a subject which she has made distinctively her own, Dr. Wolff gives an account of her more recent work in establishing criteria for the psychological assessment of normal and abnormal subjects by study of the lines, creases, and papillary ridges of the palm of the hand and of the general physical characteristics of the whole hand.

The human hand, with its unique endowments of mobility and tactile sensitivity, is one of the principal means by which the developing infant acquires knowledge of his own body and of the surrounding world and makes his individual impact upon it. In becoming the channel both for sensory impressions and for self-expression, the hand, she believes, becomes stamped with the signs of the individual's personality; and she claims that the study of it can usefully supplement formal intelligence tests with information about personality and temperament. She lays particular stress on the endocrine factors shown in the hand, which she has studied in the endocrine clinic of Dr. S. L. Simpson at Willesden General Hospital, and considers that diagnosis of these offers an easy route to understanding the patient's endocrine—and hence his emotional—make-up.

The extent of the information about personality and temperament which can be obtained by her methods, and an outline of the technique employed—though Dr. Wolff says that this cannot be simply learnt from a book—are discussed, and the latter half of the book describes her findings in the hands of mentally defective children and adult psychotics. She has studied over 600 mental defective cases, and 245 schizophrenics, 80 paraphrenics, 80 manic-depressives and 80 epileptics, in all cases with normal controls. She finds significant differences, many of them not hitherto described, both from the normal and between different types of case. The results are summarised in tables and graphs, and there are plates of hand-impressions and photographs of typical abnormal and normal hands.

In the final chapter, Dr. Wolff gives an interesting example of the validity of her brief assessments of personality by comparing, in parallel columns, her findings in 19 high-grade defective boys with those of their medical superintendents, and in 25 normal schoolgirls with those of their school-teacher who based her report on their school record four years later. These separate assessments show a very convincing agreement with Dr. Wolff's.

Rheumatism and You

A Handbook for the Rheumatic Sufferer. British Rheumatic Association: London. 1951. Pp. 70. 5*s.*

THIS little book, edited by Dr. Francis Bach, chairman of the rehabilitation committee of the British Rheumatic Association, should have a wide appeal, since, as the editor points out, there are few inhabitants of this island who have not already suffered, or will not suffer sooner or later, from some manifestation of that variety of conditions collectively and conveniently called "rheumatism" by doctors and lay men alike. It is a symposium of short sections, each written by an expert, giving advice and guidance for all types of rheumatic sufferers, and addressed directly to them. The section on home therapy gives clear and unmistakable directions for different methods of applying warmth at home for the relief of pain. The disabled, whether with crippled limbs or damaged hearts, are fully informed of the services, both official and voluntary, through which they can get help, from such things as "meals on wheels" for the housebound, to training and reablement for those who can work in spite of disability. Fatigue, worry, and anxiety are given due prominence in the ætiology of a rheumatic attack, but—rather surprisingly—nothing is said about such factors as damp and overcrowded houses or damp beds.

Vitamins

A Digest of Current Knowledge. LESLIE J. HARRIS, SC.D., D.SC., PH.D., F.R.I.C. London: J. & A. Churchill. 1951. Pp. 244. 15*s.*

FOR those who wish to pin them down in print the race against the vitamins is always a ding-dong affair. Dr. Leslie Harris, in this little volume, has done wonders, reviewing the whole subject in brisk clear sentences, well illustrated with photographs, graphs, and structural chemical formulæ. Most of the references in the text end at 1947, but an addendum gives the stop-press news up to 1950. Practitioners who feel that in recent years the vitamins have been getting a lead on them will be glad to put on a spurt with the help of this clear and quickly read little book.

Clinical Pediatric Urology

MEREDITH CAMPBELL, M.S., M.D., F.A.C.S., professor of urology, New York University Post Graduate Medical School. Philadelphia and London: W. B. Saunders. 1951. Pp. 1113. 90*s.*

THIS long book deals mainly with those genito-urinary diseases of infancy and childhood which can be treated by surgery: there is also a section on nephritis. It could have been the world's most authoritative textbook on these conditions, but in this it fails because quantity has sometimes been substituted for quality. Professor Campbell has unrivalled and unique experience, as well as command of a vast wealth of clinical material; the book is well illustrated with many excellent photographs and reproductions of X-ray films, and statistics from thousands of post-mortem examinations are quoted. But the style is far less satisfactory: take for example the statement that "in obstructive uropathy, urinary back pressure is the sum of the renal excretory pressure plus the hydrostatic pressure, the gravitational element of which will vary slightly with change of position of the patient, and the total fluid mass weight. and will depend on the volume capacity of the involved urinary channels and their tonicity." Sometimes the author seems unaware of the meaning of the words he is using, as when he speaks of "intra-vascular dissection with due care to avoidance of the vessels." Some of his advice, too, would be regarded as dangerous by most urologists: the treatment of anuria, for instance, is said to be "ureteral catheterisation to identify and—or relieve existant obstruction, and the administration of a large fluid intake, chiefly intravenously, employing physiological saline and 5% glucose or $^1/_6$ molar sodium R lactate." Surely the guiding principle of treatment here should be to preserve the child's water and electrolyte balance; for pulmonary œdema is a danger to be guarded against, and over-hydration may be fatal. Bull, Joekes, and Lowe's work, and their strikingly successful treatment of anuria and the uræmic state by the elimination of protein feeding and the administration of peanut oil and glucose through a stomach tube, is not mentioned.

This book has great potentialities; but we hope that the next edition will be more carefully edited.

Kreislaufuntersuchungen am Menschen mit fortlaufend registrierenden Methoden

K. MATTHES, professor of medicine, University of Erlangen. Stuttgart: Thieme. Pp. 326. D.M. 48.

Professor Matthes has worked for many years with apparatus which permits simultaneous and continuous recording of pulse-rate, respiration, blood-pressure, volume of finger or ear, and oxygen saturation in finger or ear. The volume curves are obtained photo-electrically by transillumination of the organ, the oxygen saturation curves by the principle used in the Millikan oximeter. With this method the influence of ordinary respiration, hyperventilation, apnœa, and breathing of high and of low oxygen concentrations on pulse-rate, blood-pressure, and peripheral circulation are investigated. Almost 100 pages deal with the action of sympathicomimetic and sympathicolytic drugs, central stimulants, and other substances, on these functions. The book contains a wealth of objectively recorded information which physiologists and pharmacologists interested in the intricacies of peripheral circulation will welcome. The many tracings are not difficult to understand, even for those with but a scanty knowledge of German, but reading would have been easier if the author had added summaries to various chapters. German, Anglo-American and Scandinavian references are ample but far from complete. The reproduction of the 205 figures is of high standard.

Psychology of C. G. Jung (London: Routledge & Kegan Paul. 1951. Pp. 204. 12*s.* 6*d.*).—The fifth edition of Dr. Jolande Jacobi's book appears five years after the fourth; there are no major changes, but the bibliography and the biographical sketch of Jung have been brought up to date. The book, translated by K. W. Bash, remains the most useful brief exposition of "complex psychology," as Jung's adherents now prefer to call the body of his theoretical teaching.

The Battle for Mental Health (New York: Philosophical Library. 1952. Pp. 105. $3.50).—This little book is written by Dr. James Clark Moloney, one of the founders of an organisation called the Cornelian Corner, named after Cornelia, the mother of the Gracchi. Founded in 1942 in Detroit, this group seeks, by research and propaganda, to end the modern practice of separating the newborn infant from the mother. Instead it hopes to introduce the practice of "rooming-in," by which the infant is placed in a crib alongside the mother's bed, and to encourage breast-feeding with opportunity to nurse whenever the infant is hungry or anxious. Dr. Moloney quotes reliable figures about the prevalence of mental illness in the United States, and the increase in crime, drug addiction, divorce, and suicide, and attributes these evils largely to modern methods of obstetric and pædiatric practice. He complains of resistance to the teachings of the Cornelian Corner, but antagonism, except among those already converted, is to be expected when these teachings are put forward with so much exaggeration as in his book.

He is no doubt correct in ascribing some of the opposition from doctors, nurses, and parents to unconscious hostility and fear of the primitive, uncontrolled impulses which they do not want to recognise in the infant—or in themselves. But when such is the case the would-be evangelist is well advised to go gently.

THE LANCET

LONDON: SATURDAY, MARCH 22, 1952

Hospital Dividends

THE last ten years have seen more changes in medicine than any previous decade. New methods of diagnosis and treatment, following one another in quick succession, have greatly altered the character of hospital work. Antibiotics, anticoagulants, muscle relaxants, cortisone, vitamin B_{12}, and the advances of cardiac surgery are but a few of the recent developments; and scientific therapeutic trials made on a previously unprecedented scale have done much to consolidate the knowledge gained. During this medical revolution the National Health Service was introduced.

The advent of the N.H.S. changed the attitude of the public towards hospital care. Previously they had recognised that hospital care, provided largely by voluntary services, was strictly limited; and many people would continue to suffer moderate inconvenience rather than bother the busy hospitals. But when the ownership of the hospitals was taken over by the nation, people began to feel that they had a right to hospital investigation and treatment. Medical propaganda also, through the press and otherwise, has made them aware of modern techniques, and many ask their doctor to send them to hospital for "an X-ray." Each year, it seems, one in fifteen of the population is admitted to hospital and one in seven attends hospital as a new outpatient; and the common experience seems to be that claims on the hospital are, on the whole, reasonable and legitimate. With this awakening public interest in medical investigation, and still more because of the increase of medical methods needing radiological and laboratory control, a great expansion has taken place in the ancillary departments in the past few years. The alarming graphs of these increases in work, previously published by Dr. FFRANGCON ROBERTS in the *British Medical Journal*, are this week presented to the public in his book *The Cost of Health*,[1] a penetrating study of the social and financial implications of modern drugs and techniques. Dr. ROBERTS asks to what extent the increase in special examinations is reflected in improved clinical results, but he does not answer this important question. There can surely be no doubt that modern laboratory and radiological techniques have on balance greatly improved the hospital service to the public, and the increase in efficiency may even be roughly parallel with the increase in the volume of such work. In routine bacteriology testing of sensitivity to antibiotics has increased the precision of their use and has thus helped to shorten the patient's stay in hospital. Anticoagulants, though they need daily blood-prothrombin estimations, appeared in one series to lower the mortality from coronary thrombosis, during the first six weeks, from about 40 to about 23%[2]; in patients with postpartum phlebitis they are credited with reducing the length of hospital care from 68 to 22 days[3]; and they have made postoperative massive pulmonary embolism a rarer complication. Accurate control of fluid balance after operation has been responsible, with improved anæsthetics and antibiotics, for a striking fall in operative mortality in recent years: for example, the mortality for acute perforation of peptic ulcer has fallen from 25 to under 4%.[4] Patients with acute renal failure from lower-nephron nephrosis, formerly a fatal condition, now recover under the Bull régime, which demands particularly careful biochemical control. Again, the routine testing of maternity patients for the rhesus factor has led to considerable improvement in the management of erythroblastosis. All these are examples of recently introduced techniques, requiring detailed laboratory studies, but paying good therapeutic dividends. Without doubt some of the increase in work is due to thoughtlessness, intellectual laziness, and lack of judgment on the part of medical staff; but it is well within the province of the pathologist to scrutinise and criticise requests coming to his department. It would prove more difficult to assess the therapeutic contribution from the greater use of X-ray examination, especially barium meals; but it is often a source of satisfaction to the patient to have the cause of his indigestion established. Patients at home can also benefit from facilities for direct pathological investigation, and this is particularly true for the diagnosis and management of anæmia and urinary infections. Today most doctors enter general practice with at least some experience of hospital work and of the scope and value of pathological and radiological methods. Though the rate of increase in the number of pathological investigations has been very great in the past five years, there is some evidence that it will diminish; and indeed there are indications that it is already diminishing. Though Dr. ROBERTS is right in pointing out that the demands of medicine are potentially unlimited, they need not therefore be wholly unrelated to common sense.

Obviously the state of the nation's finances will not allow the previously unlimited rate of expansion to continue; for the cost of illness, at present-day prices, can prove no less of an embarrassment to the State than to the individual. The N.H.S. came at a time not only of great growth in medical knowledge but also of a general rise in costs, which has now put hospital medical care well beyond the scope of voluntary support. In this connection it is instructive to read of the American experience reviewed on another page by Professor TITMUSS. In a survey of 455 Californian families, 6% of the total income went on medical care and $1^1/_2$% on dentistry. At all income levels there were families which spent over half their yearly income on medical bills; and Professor TITMUSS points out that, whatever its faults, the N.H.S. in this country must have prevented many disasters from serious illness among families at almost all social levels—in this respect, at least, serving as an instrument of preventive medicine. In its first few years the system of budgeting, although slow and clumsy, nevertheless made some provision for an expanding service, and the real limiting factors were steel, bricks, and mortar. But with a ceiling imposed on hospital expenditure further expansion of medical work can be achieved only through retraction elsewhere, by further streamlining of effort, by simplification of techniques, by shortening of length of stay in hospital, and by consultants' vigorously supervising investigations. At the same time it must be remembered that hospital services cannot be assessed simply in terms of economic advantage, for these are deeply interwoven with humanitarian considerations.

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[1] The Cost of Health. By FFRANGCON ROBERTS, M.D. London: Turnstile Press. 1952. Pp. 193. 16s.

[2] Tulloch, J. A., Gilchrist, A. R. *Brit. med. J.* 1950, ii, 965.

[3] Ball, K. P. *Proc. R. Soc. Med.* 1948, 41, 26.

[4] Avery Jones, F., Parsons, P. J., White, B. *Brit. med. J.* 1950, i, 211.

Dr. **Roberts** holds that " potentialities determined by research now exceed actualities determined by economics " and that there is therefore no economic future in expansion. But if it is true that some discoveries may create new social problems, others will afford appreciable economic relief. The flexibility of the British way of life should surely permit us to maintain an equilibrium in the face of medical progress.

Corsets and Chlorosis

One of the mysteries of 20th-century medicine is the disappearance of chlorosis, the iron-deficiency anæmia affecting girls at puberty, which in our grandfathers' time was the commonest form of anæmia seen in hospital or private practice. The iron-deficiency anæmia of women is still the commonest anæmia in Western Europe and North America ; but this syndrome is quite different from chlorosis. Chlorosis affected particularly young girls between 14 and 17 years of age ; the patients were of normal build, and wasting was not a feature though some were described as " asthenic." The extraordinary greenish facial complexion, from which the disease got its name, contrasted with the white pallor of the body and limbs. These young women suffered from fatigue out of proportion to the anæmia ; they were unduly nervous and were classically liable to fainting attacks. The appetite might be oddly perverted : schoolgirls ate blackboard chalk, for example. Obstinate constipation was common. Menstruation was scanty or suppressed, sometimes not appearing till the 18th year. Hydræmia was usually evident, with a puffy face and swollen ankles ; and venous thromboses, particularly of the femoral veins, were not uncommon. The anæmia responded promptly to treatment with iron, and relapses were rare after the age of 25 ; but the patient sometimes retained " an inclination to fainting " long after adolescence.

What caused chlorosis ? Why did it disappear abruptly from the medical scene in the first decade of this century ? May we live to see it again ? Dr. **Emil Schwarz** [1] has re-examined these questions in the light of present-day knowledge. Chlorosis was first described, he says, as long ago as 1554 by **Johannes Lange** [2] who lived in Flanders, and whose account of it as *febris alba, febris amandi* covers two of the main features. The name chlorosis was given to the disease in 1620 by **Varandeus**, of Montpellier. Thereafter the disease remained common, but it flourished most profusely in the latter half of the 19th century. **Von Noorden** devoted 200 pages to it in his section of **Nothnagel**'s textbook, published in 1897, and he quoted 285 papers published between 1879 and 1896. In 1900 at the St. Georg Hospital, Hamburg, there were 176 cases of chlorosis, 10 of pernicious anæmia, and 16 of other anæmias. Then, in little more than a decade, the disease disappeared. In 1910 the St. Georg Hospital recorded 25 cases of chlorosis, 10 of pernicious anæmia, and 50 of other anæmias. At Boston **Cabot** saw 52 cases of chlorosis in 1899, 1 in 1905, and 3 in 1906 ; in Vienna **Schwarz** himself did not see a single genuine case of chlorosis after 1910. Similarly in England, France, Italy, Spain, Scandinavia, and Poland the figures fell quite suddenly.

The ætiology had been debated for years. Nutrition did not seem to be important ; the patients were not typically wasted, and the disease affected rich and poor alike. It disappeared from the relatively poor countries of South and East Europe as it did from England, Scandinavia, and the U.S.A. ; and in Central Europe during the war of 1914–18 the poor nutrition did not bring it back. Today young girls still eat too many sweets, buns, and the like ; but they do not get the chlorosis syndrome. Abnormality of gastric secretion is not important ; less than 20% of investigated cases had achlorhydria. Likewise living conditions seem to have had little bearing on the incidence ; chlorosis disappeared in both the well and the poorly housed. The modern pursuit of exercise has been suggested as a cause of this disappearance ; but, as **Schwarz** points out, only the few were able to lie about, and the majority who had to attend to the chores of house and field were equally affected. In 1554 unsatisfied sexual desire was given as a cause, and up to modern times early marriage was advised ; but most of the victims of chlorosis were only 14 or 15 years old at the onset.

The only social habit that fills the bill—namely, one applying only to women, introduced in the 16th century and dropped in the early 20th century—is the wearing of the tightly laced and boned corset. **Schwarz** consequently devotes much space to this fashionable device and its effects. The stiff laced corset was first worn by the women of wealthy Florentine families in the early 16th century ; and by 1554, when **Lange** wrote his classical description, the fashion was well established among the well-to-do families of Flanders, as contemporary portraits show. The corset remained an essential article of feminine attire until the Napoleonic and Regency times when, for a space, fashion favoured a form of dress that did not need the foundation of a corset ; and it is interesting that medical reports of this time reflect slackening of interest in chlorosis. But in the 1820s the corset was reintroduced, and its lacing became more and more tight as fashion moved towards the " wasp waist " of the last decades of the 19th century. This was not limited to the well-to-do : in 1880 we find **Dyce Duckworth** fulminating against the unphysiological restrictions of the corset ; it was, he said, grievous to reflect that, by servile imitation of the upper class, women " in the lower orders " were also made to suffer. The laced corsets were worn from the age of 14 upwards, and we know that it was this group that had chlorosis. In 1900, however, the pliable belt came into use, and this soon ousted the lace and stay corset ; corseting of young girls rapidly went out of fashion, and by 1910 had ceased ; it has not been reintroduced, and chlorosis has been seen no more.

Physicians have denounced the laced corset since the time of **Ambroise Paré**, and from the 1850s onwards the condemnation swelled to a chorus. Oddly enough, however, only some physicians condemned the corset because it caused chlorosis. Their wrath was mainly directed against the anatomical abnormalities. The tightly laced corset with the small waist forced the diaphragm up into the expiratory position and decreased the capacity of the lungs; the liver was pushed down and pressed down the stomach and duodenum with it; the small intestine and the colon were pushed down on to the pelvic floor, and the depressed pelvic floor carried the genital organs with it. Probably the vagal and sympathetic innervation to these organs was seriously disturbed, since so many of the symptoms—like the recurrent fainting—were of vasovagal type. It is, however, not certain how these abnormalities produced anæmia. From such evidence as there is, it seems likely that defective absorption of iron in the alimentary tract was the cause, and that the anatomical distortions must have contributed to this disturbance. Schwarz points out that "the history of fashion gives accurate data for the introduction, spreading and discarding of lacing, coinciding with the peaks and troughs of chlorosis frequency"; and he notes that the fashion of lacing meets the requirements, not of a sole ætiological factor, but of a "releasing factor" —a factor that will produce the syndrome in predisposed persons. The lacing factor was limited to females, was active at puberty, and disappeared simultaneously in many countries and climates. Schwarz quotes a saying of Sherlock Holmes: "It is an old maxim of mine, that when you have excluded the impossible, whatever remains, however improbable, must be the truth"; and he concludes by saying: "Let us not overestimate the issue and proclaim the corset theory as the truth, but accept it at least as the probability remaining after we have excluded all other suggestions as downright impossible."

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[1] Schwarz, E. Chlorosis : a retrospective investigation. *Acta med. belg.* suppl. 1951.

[2] See Major, R. H. Classic Descriptions of Disease. Springfield, 1932.

Schwarz's monograph is, so far as the evidence allows, convincing; and he deals effectively with the many objections to the corset theory that have been voiced from time to time. There is certainly enough here to make all medical men determined that, whatever the vagaries of fashion, they will strenuously oppose the use of the tightly laced corset for young girls under 19; and there is also good reason for young adult women avoiding them. With a population now health-conscious, physicians' opposition is likely to be more successful than it was in the 350 years up to the start of this century.

Metabolic Rôles of Carbohydrate

Physiologists have long known that muscles achieve greater efficiency, and are less prone to fatigue, when they are metabolising carbohydrate than when they are metabolising fat. Douglas and Koch[1] found that in subjects who took a 10-mile walk ketonuria ensued unless a high-carbohydrate diet had been eaten for one or two days before the test, or unless 50 g. glucose was swallowed in divided doses during the walk. These procedures increased carbohydrate utilisation; but no such effect was observed if the 50 g. glucose was taken either 70 minutes before or immediately before the exercise, presumably because it was converted into some form in which it could no longer be used as energy. This situation may perhaps be explained by Mirski's[2] finding that in rats glycogen formation in adipose tissue was consistently correlated with enhanced fat deposition, from which he inferred that glycogen was probably an intermediate stage in the transformation of carbohydrate to fat. Furthermore, glycogen in adipose tissue cannot be regarded as an additional carbohydrate store for replacing the blood-sugar, since no glucose is formed when this glycogen breaks down. The phosphorolytic breakdown in white fat differs from that in muscle and liver in that fatty tissue contains no phosphoglucomutase to convert glucose-1-phosphate to glucose-6-phosphate and also lacks the enzyme which converts glucose-6-phosphate into glucose. The brown interscapular fat of rats contains phosphoglucomutase; but adult man, whose fat is metabolically less versatile, has nothing analogous to the brown fat or "hibernation gland" of lower mammals.[3] In the fat depots glycogen has been proved to be an intermediate stage in fatty-acid synthesis by the finding of respiratory quotients well above unity when glycogen is present,[2] and by in-vitro studies[4] on adipose tissue incubated with serum enriched with deuterium oxide; fatty acids were then formed which contained stably bound deuterium. Similar isotope studies[5] have finally disproved the old theory that fat is deposited in adipose tissue only when given in excess of the caloric requirement; for 50% of the ingested deuterium was found in the fat stores four days after feeding, even when there had been no change in the total quantity of body-fat—or indeed during fasting. Stetten and Boxer[6] have emphasised the importance of the metabolic pathway of carbohydrate through fat; they found that in the normal rat ten times more fed carbohydrate is stored as fat than as glycogen. In alloxan-diabetic rats, however, only 5% of the normal amount of carbohydrate is converted into fat.[7] Adipose tissue participates in fat synthesis, and insulin is necessary for normal glycogen and fat deposition in such tissue; so any delay of metabolism in this tissue may be important in the pathogenesis of rare forms of human diabetes.

Clinically of no less interest is the relation of carbohydrate to protein metabolism. Advantage is taken of the nitrogen-sparing action of a high-carbohydrate diet in the sugar-oil-water emulsion treatment of uræmia developed by Bull and his colleagues[8]; but its mechanism is by no means clear. It is known that the nitrogen sparing or storing effect of a single carbohydrate meal is related to the time between the consumption of the protein and that of the extra carbohydrate[9]; and Geiger[10] found that the growth of young rats was likewise affected by the temporal separation of the feeding of protein from that of the remainder of the diet. Nitrogen metabolism is undisturbed by dissociating only a part of the dietary protein from the carbohydrate,[11] whereas nitrogen loss ensues when the protein and carbohydrate moieties are completely separated. On the other hand, the association of a small amount of carbohydrate with the protein of the day does not necessarily maintain normal protein

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1. Douglas, C. G., Koch, A. C. E. *J. Physiol.* 1951, 114, 208.
2. Mirski, A. *Biochem. J.* 1942, 36, 232.
3. Wertheimer, E., Shapiro, B. *Physiol. Rev.* 1948, 28, 451.
4. Shapiro, B., Wertheimer, E. *J. biol. Chem.* 1948, 173, 725.
5. Schoenheimer, R., Rittenberg, D. *Ibid*, 1935, 111, 163.
6. Stetten, D. jun., Boxer, G. E. *Ibid*, 1944, 155, 231.
7. Stetten, D. jun., Kleiner, B. V. *Ibid*, 1946, 162, 377.
8. Bull, G. M., Jockes, A. M., Lowe, K. G. *Lancet*, 1949, ii, 229.
9. Cuthbertson, D. P., McCutcheon, A., Munro, H. N. *Biochem. J.* 1940, 34, 1002.
10. Geiger, E. *Science*, 1948, 108, 42.
11. Cuthbertson, D. P., Munro, H. N. *Biochem. J.* 1939, 33, 128.

metabolism. Nitrogen-sparing and nitrogen-saving differ in certain respects.[11] Nitrogen-sparing occurs when normal quantities of carbohydrate and protein are ingested together; and its onset is immediate. The sparing is equally distributed between night and day and is not necessarily proportional to the amount of carbohydrate present with the protein. Nitrogen-saving by excess carbohydrate differs in that ingestion at any time of extra carbohydrate can in the long run cause nitrogen storage; but the full effect does not appear for several days. The nitrogen-saving is mainly effected on the day excretion of nitrogen, even if the carbohydrate is taken at night; and the nitrogen thus stored is roughly proportional to the amount of extra carbohydrate taken. That the nitrogen loss which follows the separation of carbohydrate and protein in the diet is probably endogenous is suggested by its relative constancy from one person to another, the quantitative similarity to the nitrogen losses on protein-free diets, and the equal nitrogen loss during day and night. Much of the nitrogen spared by carbohydrate is probably stored in the liver,[12] in which the various protein fractions increase equally.[13] The unusual lability of these hepatic protein stores was demonstrated by Addis and his group,[14] who found that in rats fasted for seven days the liver lost 40% of its protein; this was much more than the proportion lost by other tissues, but in view of their greater bulk these other tissues contributed about four times as much as the liver towards making good the total protein deficit.

Of the many hypotheses purporting to explain the nitrogen sparing and saving effects of carbohydrate, most have been proved groundless. That this is not merely a calorie-sparing effect is shown by the ineffectiveness of substituting calorically superior fat for carbohydrate.[15] Nor is there any reason to believe that carbohydrate improves the intestinal absorption of protein[15 16] or facilitates protein utilisation by providing the necessary precursors of missing non-essential amino-acids.[17] Excessive combustion of protein ingested alone, due to its own specific dynamic action, is unlikely.[11] The possibility that dietary sugar might mobilise insulin, which is known to have a nitrogen-sparing effect, was investigated by Bancroft and his colleagues[18]; but even in diabetic rats sugar still spared nitrogen. Certain anterior pituitary extracts have a nitrogen-sparing action, but these workers showed that the pituitary gland need not be present for carbohydrate to spare protein. There remains the hypothesis that carbohydrate has a specific inhibitory action on the deaminases of the body[11]—an action which would not come into play unless both carbohydrate and protein were simultaneously ingested. This would explain why it is urea excretion that is mainly spared by carbohydrate, and could also account for the nitrogen sparing and saving effects. Some experimental evidence for this mechanism was described by Krebs,[19] who showed that deamination by liver slices is inhibited by the presence of easily oxidisable substance such as lactate, pyruvate, succinic, and α-keto acid (but curiously enough not glucose).

Although far-reaching in its effects, the basi mechanism of carbohydrate-protein relations remain largely unsolved. But the most general explanation for which there is considerable indirect evidence,[2 suggests that carbohydrate provides a temporar increase in the level of available energy, and mor specifically of adenosine triphosphate, with consequen stimulation of protein synthesis.

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[12] Cuthbertson, D. P., Munro, H. N. *Ibid*, 1937, 31, 694.
[13] Luck, J. M. *J. biol. Chem.* 1936, 115, 491.
[14] Addis, T., Poo, L. J., Lew, W. *Ibid*, pp. 111, 117.
[15] Munro, H. N. *J. Nutrit.* 1949, 39, 375.
[16] Geiger, E., Bancroft, R. W., Hagerty, E. B. *Ibid*, 1950, 42, 577.
[17] Geiger, E. *Science*, 1950, 111, 594.
[18] Bancroft, R. W., Geiger, E., Hagerty, E. B. *Endocrinol.* 1951, 49, 149.
[19] Krebs, H. A. *Biochem. J.* 1935, 29, 1620.

Annotations

THE THYROID HORMONE

Two brief papers by Dr. Gross and Dr. Pitt-Rivers—of which the first appeared on March 1 and the second i published in this issue—have given a fresh twist to th long controversy about the nature of the circulatin thyroid hormone. When thyroglobulin was isolated just before the turn of the century, it was naturall supposed that this protein was not only present in th thyroid gland but also circulated in the blood. Whe thyroxine was isolated from the breakdown products o thyroglobulin and was shown to be physiologically active it became possible to imagine that this amino-acid wa the actual hormone. Certain difficulties (which do no now seem very real) made this idea hard to accept and so it was thought that the hormone was probably a polypeptide containing thyroxine—a sort of half-way stage between thyroglobulin and thyroxine. But th more stringent analysis of iodine-containing compounds, made possible by the use of radioactive iodine, produced no evidence in favour of this idea; and by 1944 Harington[21] was ready to discard it in favour of the simpler hypothesis that thyroxine is itself the thyroid hormone.

Gross and Pitt-Rivers began their work with an analysis of the iodine-containing compounds in human plasma, using the method of paper chromatography. The plasma came from patients under treatment with radio-iodine, and the presence of the iodine-containing compounds was revealed by developing the chromatograms on photographic film. When the plasma came from patients who had received radio-iodine a few days previously, the characteristic imprint of thyroxine was readily detected. Nearby was another image, indicating an unknown iodine-containing substance which appeared in the plasma at about the same time as thyroxine. This started a chemical chase, ending in the identification of the substance as triiodothyronine (thyroxine less one iodine atom). If the work had stopped at this point it would have occasioned mild interest, but no great surprise. Triiodothyronine might well be pictured as incompletely formed thyroxine, or thyroxine in the early stages of decay. Now, however, it appears that the new compound not merely has the physiological properties of thyroxine but is actually more potent. So far the comparison has been made by only one physiological reaction—the ability to prevent goitre in rats treated with thiouracil. It will clearly be necessary to compare the two compounds in a variety of physiological situations, including among others that classical test-animal—the patient with myxœdema. Only then can we be certain that a compound of greater activity than thyroxine has been discovered. But if this proves to be so, it will be difficult to resist the idea that triiodothyronine is the thyroid hormone. This compound is known to be present in the thyroid as well as in the blood, and its action might account for the puzzling observation that thyroid extracts are sometimes more active physio-

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[20] Munro, H.N. *Physiol. Rev.* 1951, 31, 449.
[21] Harington, C. R. *Proc. roy. Soc.* B. 1944, 132, 223.

logically than their thyroxine content would suggest. Possibly, too, this work may clear up the old mystery of the long time-lag before thyroxine produces its characteristic effects; for it may have to be converted to triiodothyronine before it becomes active. Though these new observations will have no immediate clinical application (for thyroxine by mouth will remain an entirely satisfactory treatment for myxœdema) they will undoubtedly have a considerable impact on the theory of how the thyroid works.

POST-STARVATION GYNÆCOMASTIA

GYNÆCOMASTIA is a bizarre abnormality distressing to the patient and often puzzling to his doctor. There are three common types, associated with adolescence, with decompensated cirrhosis of the liver, and with obvious endocrine disorders. Enlargement of the breasts is also seen in men treated with œstrogens, gonadotropins, or methyl testosterone; and in patients with Addison's disease after treatment with adrenal hormones. The exact nature of the hormonal imbalance which stimulates the male breast to proliferate is obscure. McCullagh et al.[1] suggested that the seminiferous tubules of the testes normally produce a hormone, "inhibin," which protects the male breast from the proliferative effects of androgens. In severe progressive liver disease gynæcomastia appears as part of a syndrome of feminisation in which the shape of the body becomes more feminine, the testes and prostate atrophy, and the male distribution of hair is lost.[2] In the normal male, the liver stabilises the androgen-œstrogen balance and inactivates free œstrogen by conjugation and esterification. Thus, the healthy man's urine contains little or no free hormone. When the liver is damaged, however, free œstrogen circulates in the blood, producing the sexual changes described, and appears in the urine.[3]

Soon after the late war epidemics of gynæcomastia were reported in rehabilitated American, British, and Canadian prisoners-of-war. The best clinical description of the condition was that of Musselman[4] who was himself a prisoner-of-war and watched the waxing and waning of breasts in American soldiers in Japanese prison-camps in the Phillipine Islands. He observed that many prisoners developed hard disc-like swellings in the subareolar breast tissue whenever the miserable camp rations were increased to a reasonable level. The transient gynæcomastia was accompanied by mild orchitis and a return of libido. Occasionally, fluid was discharged from the nipples. Klatskin et al.[5] reported transient gynæcomastia in 16% of American soldiers repatriated from prisoner-of-war camps in the Far East. They suggested that the breast changes might be the result of liver damage caused by the tropical diseases common in these camps. A sharp rise in the incidence of gynæcomastia in healthy adults was seen in Germany in 1946–47, when food became more plentiful.[6] This was not associated with any gross liver disease, and the histological appearances of the enlarged breast tissue was apparently different from the proliferation usually caused by excess of œstrogen. The evidence suggests that the gynæcomastia of prisoners-of-war is a distinct clinical entity which appears when the very poorly nourished are adequately fed. If so, we should expect enlargement of the breasts in a small proportion of men recovering from debilitating diseases, such as sprue, anorexia nervosa, thyrotoxicosis, or severe diabetes. Kark et al.[7] have, in fact, reported 9 cases of cirrhosis of the liver in which gynæcomastia appeared during treatment with high-protein, high-calorie diets. Their patients were all severely undernourished men who had been heavy drinkers. While under observation in the metabolic unit they steadily put on weight and remained in positive nitrogen balance. Nutritional repair and improvement in liver function were shortly followed by a return of libido, growth of hair of male distribution, enlargement of the testicles, and nocturnal emissions; gynæcomastia appeared for some weeks, after which the breasts returned to normal. Masculine characteristics were finally restored.

This "refeeding" gynæcomastia, which appears and disappears during the rehabilitation of cirrhotics, differs from the œstrogenisation which produces the permanent gynæcomastia seen in men going downhill with progressive liver disease. Kark suggests that the inclusion of arginine, an amino-acid essential to normal spermatogenesis, in the diet of men suffering from cirrhosis or starvation might reveal the mechanism of refeeding gynæcomastia.

SAVINGS ON THE N.H.S. DRUG BILL

IT takes two to make a quarrel; and much the same can be said of a prescription. Both the number and the average cost of prescriptions under the National Health Service have been rising steadily. On the patient's side a check is to be applied in the form of the 1s. charge; and the Ministry of Health, hoping no doubt that doctors, for their part will impose a similar restraint on themselves, is to issue periodical bulletins describing the outstanding facts about costs (see p. 622). Certainly a respectable amount of money could be saved by more efficient and less wasteful buying, prescribing, and dispensing of drugs.[8]

One suggestion, made in the report of the Anglo-American productivity team, was that liquids should be sold by volume instead of by weight, as they now are. A hospital pharmacist ordering a winchester of some drug would then know that he would get $^1/_2$-gallon (2·5 litres), instead of something between 4 and 7 lb., depending on the specific gravity of the liquid. Buying tincture of opium, for example, by weight and then dispensing it by fluid measure is wasteful of time and effort. Some drug manufacturers say that if sale by volume was generally adopted they would reduce their prices substantially because of the saving on clerical costs. Instead of charging for liquids by the lb., plus a charge for the bottle, the manufacturer could quote for a standard winchester including the cost of the bottle. At the moment winchesters vary in content from 60 to 120 fl. oz. If 90 fl. oz. was accepted as the standard, the present wide range of bottles could be discarded and stock-shelf space would also be saved. Packing bottles for export could be simplified by using standard crates; and there would be a saving on invoicing because "so many winchesters of syrup of orange" would suffice.

The use of two measures, apothecaries and metric, obviously causes unnecessary trouble. The British Pharmacopœia Commission and the Pharmaceutical Society have for a long time advocated the adoption of the metric system only. The doses of the more modern drugs are usually stated in the metric system already, and we are getting used to writing "0·5 g." for the tablets of sulphonamides, even if we feel closely tied to "gr. 10" when it comes to aspirin. After a little practice with a ready-reckoner we might view the change-over in a truer perspective and even forget our ingrained prejudices—or we might not. Another suggestion is that all official preparations should be compounded so that the usual dose is one tablet, one ampoule, or 1 ml. The principle

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1. McCullagh, E. P., Schneider, R. W., Bowman, W., Smith, M.B. *J. clin. Endocrinol.* 1948, 8, 275.
2. McCullagh, E. P., Rossviller, H. R. *Ibid*, 1941, 1, 496. Lloyd, C. W., Williams, R. H. *Amer. J. Med.* 1948, 4, 315. Bennett, H. S., Baggenstoss, A. H., Butt, H. R. *Amer. J. clin. Path.* 1950, 20, 814.
3. Glass, S. J., Edmondson, H. A., Soll, S. N. *Endocrinology*, 1940, 27, 749; *J. clin. Endocrinol.* 1944, 4, 54.
4. Musselman, M. M. *War Med.* 1945, 8, 325.
5. Klatskin, G., Salter, W. T., Humm, F. D. *Amer. J. med. Sci.* 1947, 213, 19.
6. Weltz, G. *Dtsch. med. Wschr.* 1950, 75, 643.
7. Kark, R. M., Morey, G. R., Paynter, C. R. *Amer. J. med. Sci.* 1951, 222, 154.
8. "Manufacturer-Wholesaler." *Retail Chemist*, 1952, 23, 55.

of simplified dosages should certainly be followed, though the wide range of dosage of some drugs would make difficulties if the scheme was generally adopted. Thus the dose of 'Artane' ranges from 2·5 to 60 mg. If the official tablet contained 5 mg. (with a groove for division) some unfortunate patients would have to swallow twelve.

An overdue reform is the deletion of useless or outmoded remedies and preparations from the B.P. and the B.P.C. Substances like bismuth carbonate, glycerophosphates, and creosote would gradually disappear from our prescriptions if they no longer received the official blessing.

Coming even nearer home, the pharmacists spend many unprofitable minutes every day deciphering almost illegible scripts. Is it not rather a slur on the medical profession that the pharmaceutical qualifying examination still includes the puzzling out of unreadable prescriptions? Now, when the patient may take his script to any convenient pharmacist—often one who has not met the calligraphy before—it seems reasonable to ask the doctor to spend the few more seconds on his prescriptions that will convey his requirements without doubt or delay to any dispenser in the land. We shall at least be saved such witticisms as: "Who wrote this? Geoffrey Chaucer?"

SLOW AT STARTING

DEANS pride themselves on spotting winners among the students who parade before them, in the course of the years; but they know they are not infallible, and they usually err on the side of leniency when they are in doubt. Present regulations, however, sometimes force their hand to some extent, and lead them to weed out a young person who only needs freeing from entangling circumstances. Such a case has recently been reported to us.

The student comes of a family with a creditable medical tradition, and has always intended to become a doctor. After getting exemption, at a good scholastic level, from matriculation, he was accepted, while at school, for training in a London teaching hospital. He still had a year to spend at school, and the hospital dean—wisely, in our view—advised him against spending it on science. He therefore worked for, and took, his Higher Certificate in arts. He has since been told that this was inviting failure.

He now came to London for the first time, and was pressed by his contemporaries to join every sort of society and to take part in every sport. None of his teachers seems to have shown anything like the same interest in his doings. A musical boy, he was now in reach, for the first time, of the best concerts in the country. He did what nine out of ten of us did in our first term at the university: he opened his mind to the new impressions crowding in on him, and made the most of the opportunity. At the end of that term, however, he realised how great was his handicap in not having spent a preliminary year on science while at school. He began to work hard, but with a sense of being at sea; and soon, feeling that failure in the first M.B. was inevitable, he took some coaching. He failed, however, and so did 7 others out of 11 who had had no previous scientific grounding. He was rejected for further medical training by the school.

He is now working at a crammer's, and finding the work well within his scope; but owing to his rejection, no hospital has so far been willing to take him on.

This seems to us a thoroughly unfortunate case. The student clearly has ability, or he would not have passed his school examinations successfully; moreover he seems to have an educable mind, not narrowly confined to his subject but widely interested—the kind of mind we need in medicine. If a year of humane studies at school is to prove a handicap instead of an asset, more and more students will specialise too soon, and enter their medical training lopsided and mentally narrowed, probably for life. It is right that on entry to their medical schools students should be warned by their deans that failure in two or more subjects in the first M.B. will be regarded as serious, and likely to lead to dismissal. But every case in which this happens should be carefully reviewed, and all young people with an arts rather than a scientific training—provided they have worked reasonably well—should be allowed a second chance. A student who has done two years' science at school and then fails dismally in his first M.B. is a horse of a different colour: most likely he will go on failing in examinations, and become a burden on the school. As he can hardly be turned out after three or four years' training he had better, for everybody's sake, be rejected at the end of his first year.

A rule is necessary, and it must be consistently applied if it is to have a properly bracing effect; but there is no reason why it should be rigid, allowing no latitude for special circumstances. A boy accepted on a *recommended* training in arts should have been offered a system of tutoring in his first year which helped him, not only to adjust to a set of new subjects and terms, but to meet the freedom of university life steadily, and without too much excitement; and since his school scholastic record was good he should have had some degree of licence over the first M.B.

PSYCHOSES IN CHILDHOOD

PSYCHOSIS in childhood is by no means as rare as an older generation of psychiatrists thought it. Twenty years ago, Melanie Klein[1] pointed out that many schizophrenic children, especially of the poorer classes, were not brought to psychiatrists, while others were classed as cases of arrested development, mental deficiency, or some psychopathic condition, or as having asocial tendencies. Because many of the characteristics and behaviour disturbances in these children differ only in degree from those seen during the development of the normal child, they are easily mistaken, in the early stages, for exaggerated examples of naughtiness, docility, or restlessness. Despert[2] came to similar conclusions as a result of her work with American children.

On March 11, at a meeting of the psychiatric section of the Royal Society of Medicine, Dr. Mildred Creak showed a film illustrating the distinctive appearance and behaviour of these children. At the onset of psychosis, the child shows an inability to form normal relations with people or objects around him. He may appear quite alert and intelligent, but his mental development comes to a standstill, or begins to regress, speech reverting to infantile babbling or being given up entirely. Sphincter control and motor skills may be lost, and the child becomes clumsy, unable to manipulate feeding tools or toys. He may give up play, or his play may become aimless, or stereotyped and obsessional, or he may stay immobile for long periods. On the other hand he may be hyperkinetic, whirling and spinning about, or grimacing, pushing out his lips or his tongue, or moving and twisting his fingers. He may seem unaware of people about him, but if they withdraw he will often cling to them. If they approach he will reject them, however, and may have an outburst of aimless rage.

Once the psychosis has become established these children fail to develop intellectually, and many of them—especially if they are noticeably odd and difficult to manage—get sent to mental-deficiency institutions. Dr. G. O'Gorman noted that this is not the result of mistaken diagnosis: schizophrenia interrupting normal mental development between birth and the age of sixteen or thereabouts may so retard a child's progress that he does in fact become a mental defective. Indeed, some adult demented schizophrenics can rightly be classed as mental defectives, for their illness, in a quarter of the cases, begins before the age of 18. In all mental hospitals there are schizophrenics who could equally logically be in a mental-defective colony. About 10% of cases of mental defect in adolescents and adults, Dr. O'Gorman believes, are the end-result of childhood schizophrenia. On the other hand, ordinary mental defectives are not likely to develop schizophrenia; those

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1. Klein, M. *Int. J. Psycho-Anal.* 1930, 11.
2. Despert, J. L. *Psychiat. Quart.* 1938, 12, 336.

who do are probably examples of relapse of an initial psychosis, after an intervening period of remission. Many of these psychotic defectives have higher intelligence quotients than ordinary defectives, but they are less educable because they are less in touch with their environment. Some of them have isolated areas of intellectual preservation; he mentioned a child who—though he could not read—after several years in a mental-defective colony could still play the piano, which he had learnt before the onset of his psychosis. Dr. D. W. Winnicott remarked that some phases in normal development can properly be termed psychotic. The young child lives in a mad world and only gradually learns to relate himself to reality: even in adults, he suggested, a retreat from the hard tasks of everyday reality-testing is allowed in the spheres of religion and art. The child analyst has to be able to enter a mad world where reality is dealt with by means of magical thinking. It may be questioned whether "psychotic" is the right term to use in discussing the phases of development; being equated with "madness" by parents and lay people, it is apt, as Dr. K. Cameron pointed out, to cause alarm and misapprehension.

Speakers had very little to offer on the subject of treatment for these serious illnesses of childhood. Good results were claimed from loving and patient parental care of a difficult and apparently unrewarding child, psychotherapy (sometimes more efficacious after electroconvulsive therapy), and long-continued psycho-analysis; but only in cases recognised early enough and treated with sufficient perseverance and intensity. Insulin, though it may improve the physical condition and so help the task of the psychotherapist, does not seem to have yielded results comparable to those seen in adult psychotics. All agreed that we must learn to recognise these cases earlier.

VIRUS VARIATION

VIRUSES are well known to vary in virulence. At a meeting of the comparative medicine section of the Royal Society of Medicine on Feb. 20, Mr. J. R. Hudson pointed out that African natives recognise mild and severe forms of rinderpest, and in protecting their animals from the severe form by exposing them to the mild they practise something approaching Jennerian methods. Similarly, as Mr. I. A. Galloway, D.SC., pointed out, the virulence of different strains of the foot-and-mouth disease viruses varies widely, and many antigenic subtypes have been uncovered. Viruses may vary, as Mr. Hudson remarked, not only in antigenic characters and virulence but in host range, tissue affinities, and physical properties; and with regard to the influenza viruses Professor Wilson Smith, F.R.S., made a plea for less preoccupation with the antigenic variations and greater attention to the other characters that might account for virulence. He described a variant of influenza virus which had been found in his laboratory, and which showed changes in its surface configuration without antigenic or other changes. Dr. D. J. Trevan and Mr. A. B. MacIntyre made it clear that the viruses of the dog distemper complex, though antigenically related, produce different clinical syndromes—notably the classical catarrhal distemper and the non-catarrhal "hard pad." The latter is essentially the distemper of recent times. This strain of virus gives rise to lesions in stratified squamous epithelium, and sometimes in the brain, which differ from those associated with the distemper virus as known to Laidlaw and Dunkin; and typical catarrhal distemper does not follow injection of it into dogs.

It is, of course, not easy to dissociate the virulence of a virus from the susceptibility of its host; there are many well-known examples of a single virus strain causing mild disease in a partially immune population and extremely severe disease in a susceptible population entering the area. When the behaviour of a virus changes on passage in a new host, it is tempting to diagnose virus variation. Other possibilities, however, must be taken into account. One is that contamination by a laboratory strain has taken place; a second is that a mixture of two agents was originally present, one of which has been selected by the new host; and a third is that inoculation with foreign material has activated a latent virus in the new host—workers with respiratory viruses and the virus of lymphocytic choriomeningitis are familiar with this difficulty. Very rigid criteria must be satisfied before altered behaviour of a virus can be ascribed to variation.

At the meeting one further type of virus variation was mentioned: Mr. Hudson suggested that the three types of equine encephalomyelitis virus—Eastern, Western, and Venezuelan—may be variants derived originally from a common ancestor. But here we are leaving the virus world for the metaphysical. M. Jourdain was delighted to learn that he had been talking prose all his life; perhaps the virologist will one day find that he has been talking metaphysics.

THE AUSTRALIAN RESIDENT

THE newly qualified medical graduate in Australia often finds it impossible to get a resident hospital appointment. This difficulty is not confined to Australia, but a report[1] by Mr. V. M. Coppleson, director of postgraduate studies in the University of Sydney, shows how acute it is in that realm. The number of doctors qualifying each year from the university is now double the pre-war figure, and the increase in internships has been quite insufficient to meet the demand. Moreover, Mr. Coppleson thinks that such vacancies as there are do not always measure up to the standard of training he would like to see in the vital first year after qualification. "No matter how good the undergraduate couse he has attended, the type of hospital in which he trains after graduation will determine the standard of medicine a medical graduate will practise for the rest of his life." The report goes on to say that in Australia today "the young graduate who has not the ability and good fortune to obtain an internship at one of the larger teaching hospitals is likely to receive a poor and inadequate training in what is undoubtedly the most important year of his career." Newly qualified doctors, as yet too inexperienced to begin the practice of medicine, are left largely to their own resources. There is no compulsory intern year after qualification in New South Wales, though legislation to introduce one was passed as long ago as 1938; its enforcement was postponed first because of war and then because of shortage of jobs. Those who can, usually do four appointments of three months each. Mr. Coppleson says that internships should be more closely supervised and postgraduate teaching more widely planned by the Australian universities than at present.

The standard that he would establish is undoubtedly a high one, compounded from the best that he has seen during a long tour last year of teaching centres in this country and the United States. The report is called Trends in Modern Medical Education, and it interprets the results of his investigations into every part of the subject in relation to Australian conditions in general and those of Sydney and New South Wales in particular. But some judgments might find wider application. For instance: "In graduate medical education a false scent is being followed. The acquisition of diplomas has become the highest goal, and instead of through the hospital, the university and the research laboratory, the path of higher medical education is being blazed through the classroom and the examination hall." No system yet devised for the specialised training of physicians and surgeons can entirely escape this recurrent criticism, but undue emphasis on academic achievement can only be avoided by some such scheme as the report suggests—namely, a "postgraduate vocational phase" after which a man's merits may be fairly estimated as much by his experience and clinical work as by examination results.

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[1] *Bull. postgrad. Comm. Med., Univ. Sydney*, 1951, 7, 111.

The shortage of suitable resident jobs in hospitals has persuaded many of the younger doctors in Australia that they would do better by going abroad for their training. Such expeditions have much to recommend them, but this is surely the wrong reason for making them. We have referred [2] to a suggestion that the interchange of postgraduate men between this country and the Commonwealth could be more profitably conducted if a representative conference formulated ways and means on a broader basis than that on which exchanges are now made. This lack of space in the teaching centres of Australia will mean that in the first instance our representatives at such a conference must be prepared to contribute a greater share of jobs to the exchange pool than is offered them. But the proposal, to which Mr. Coppleson's evidence gives further support, should not be discredited if the early traffic is largely in one direction. Our coöperation in an extension of present arrangements will not only help to relieve the congestion in Australia, but by doing so it will simplify the practical application of the report, should its recommendations find general acceptance.

PRIMARY PULMONARY HYPERTENSION

IN a small proportion of cases of pulmonary hypertension [3] no cause can be found. Nowadays catheterisation of the right heart enables clinicians to diagnose primary pulmonary hypertension with confidence; and it is evidently less rare than was thought. Dresdale et al.[4] draw attention to a characteristic clinical syndrome in this disorder; the salient features are

> "exertional weakness and dyspnœa in patients who subsequently develop progressive right heart failure without antecedent cardiac or pulmonary disease. Effort syncope and angina are most significant when present. Sudden death is not infrequent. The pertinent physical findings are a normal systemic blood pressure, clear lungs, an accentuated pulmonic second sound and the variability or absence of heart murmurs. Venous distension and hepatomegaly occur unassociated with peripheral œdema or ascites except late in the course of the disease. Cyanosis, when encountered, is a terminal feature unless the disease is complicated by a patent foramen ovale. This syndrome has been seen in both sexes at all ages but is most common between the ages of twenty and forty years."

Electrocardiography shows right ventricular hypertrophy and normal rhythm; and radiographs reveal right ventricular enlargement, a bulging pulmonary artery, prominent hilar vessels, and normal or diminished vascular shadows in the lung fields. In primary pulmonary hypertension hypertrophy of the right ventricle is constantly found, but there are wide variations in the nature, severity, and distribution of the obstructive vascular changes in the lungs proximal to the capillary bed. The evidence from post-mortem and hæmodynamic studies suggests that the increased resistance is situated in the small pulmonary arteries. As McKeown [5] has pointed out, however, the interpretation of pulmonary vascular lesions, especially in the later decades, is particularly difficult because in "normal" controls there is nearly always some pulmonary atherosclerosis; and this might explain the widely varying findings in primary pulmonary hypertension.

The symptoms of weakness, syncope, and anginal pain on effort are of some interest. In these cases the right ventricular end diastolic pressure during exercise is high; this gives rise to acute right heart insufficiency with resultant inadequate filling of the left ventricle, causing temporary cerebral anæmia and syncope, reminiscent of effort syncope in aortic stenosis. The high diastolic pressure in the right ventricle could impede the coronary flow (normally greatest during diastole) and so account for the effort angina. The mechanism of chest pain in pulmonary hypertension is still undecided. Viar and Harrison [6] give good reasons for supposing that its most likely cause is distension of the pulmonary artery, for pain has not been noted in Fallot's tetrad, where the pulmonary arterial pressure is low, yet it is common in atrial septal defect, Eisenmenger complex, and patent ductus arteriosus. The pain of pulmonary embolism may be of similar origin. Viar and Harrison observe that this pulmonary hypertensive pain is identical in character and location with the pain of coronary disease, but can usually be distinguished from it by its rather longer duration and the greater frequency of accompanying dyspnœa, by its aggravation on hyperventilating and its relief on inhaling oxygen, and by the constant evidence of right ventricular hypertrophy.

Primary pulmonary hypertension is analogous in many fundamental features with essential systemic hypertension. These conditions both have in common an unknown ætiology; increased tone of precapillary arterioles, whose histological pattern ranges widely from normal to obliterative arteriosclerosis; ventricular hypertrophy; and finally evidence of autonomic nervous system overactivity. Thus Dresdale et al.[4] found that parenteral injections of 'Priscoline,' an adrenolytic and sympatholytic agent, distinctly lowered the pulmonary artery blood-pressure in these cases—a reaction which they deemed specific to pulmonary hypertension, though Cournand [7] does not agree with this. If in time the rôle of vasomotor activity in primary pulmonary hypertension is established, the day may not be far off when this disease will be treated by thoracic sympathectomy.

IT'S A BOY

To those unwilling to wait a few weeks for Nature to reveal the answer, the work of Rapp and Richardson on prenatal sex-determination will be of interest. Their preliminary observations [8] have emerged from applying to saliva the Richardson pregnancy test,[9] which depends on the presence in the woman's urine of free œstrone (in contrast to bound or modified œstrone or similar 17-ketosteroids). The level of free œstrone substances rises sharply soon after conception; and the test is positive as little as two weeks after conception and sometimes even before the first missed menstrual period. Rapp and Richardson now report that with saliva the test was positive in only some of the women who were in their sixth or seventh month of pregnancy, although in all cases free œstrone was present in the urine. In nearly every case, however, the positive saliva tests were associated with a male child, and most of the negative results with a female child. Of 221 male births, the saliva test was positive in all but 3; conversely, of 155 female births the test was negative in all but 7.

The exact cause of the positive test is unknown; but Rapp and Richardson suspect that it may be some androgenic substance, since a non-gravid female normally yields a negative test but may give a strongly positive reaction after the injection of testosterone or androsterone. Furthermore, male saliva, blood-serum, and spermatic fluid are strongly positive. It seems that in women salivary glands exert delicate selectivity by screening out certain female-associated hormones but allowing certain male-associated ones to pass.

DR. G. W. M. FINDLAY, editor of the abstracting service of the British Medical Association and formerly a member of the scientific staff of the Wellcome Research Institution, died on March 14 at the age of 59.

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[2] *Lancet*, Jan 5, 1952, p. 41.

[3] Leading article, *Ibid*, 1951, i, 621.

[4] Dresdale, D. T., Schultz, M., Michtom, R. J. *Amer. J. Med.* 1951, 11, 686.

[5] McKeown, F. *Brit. Heart J.* 1952, 14, 25.

[6] Viar, W. N., Harrison, T. R. *Circulation*, 1952, 5, 1.

[7] Cournand, A. *Ibid*, 1950, 2, 641.

[8] Rapp, G. W., Richardson, G. C. *Science*, 1952, 115, 265.

[9] Richardson, G. C. *Amer. J. Obstet. Gynec.* 1951, 61, 1317.

Reconstruction

THE COST OF MEDICAL CARE

American Experience and the N.H.S.

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THE social thinking of the 1930s was strongly attracted o the concept of prevention, in its application to the ealth of the individual and of society as a whole. dvances in medical science and in the diagnosis and reatment of disease had brought into sharper focus the ulf between what was and what might be in states of ealth among different sections of the population. "We nust prevent, for we now know that much is preventble," said those who were not content with things as hey were. It followed then, according to this argument, hat a prerequisite to preventive action was the reform f what Lord Horder once called "the maze, the nwieldiness, the overlap, the uneconomy, the lack of ntegration of our health services." This was one barrier o prevention; a second was money, which often stood etween the patient and the doctor.

With the coming of the National Health Service the irst barrier was lowered and the second was swept way. Paradoxically, however, we now hear less about revention—less about early consultation with the loctor, and more about needlessly wasting the doctor's ime. Such a swing of opinion might be described as he substitution of sober realism for cloudy romanticism bout "positive" health; but this would be no sufficient xplanation. Many factors have contributed to the change in outlook, and among these the present-day cost of medical care must be counted as one of the most influential. The impression is now widespread that we are spending too much on our health services and that the way in which these services are organised has led to excessive expenditure, over-consumption of medical care, and inordinate drug-taking. Concerned as we now are to reduce these costs, it is not perhaps surprising that less is heard about the prevention of ill health.

The National Health Service now stands at a critical point in its history. Like the impatient gardener, we are tempted to uproot it before it has had time to grow to maturity. Before we take any action whose cumulative results we may later regret, it would be wise to seek out some hard facts. What evidence is there that the health service, by itself and as a means by which doctor and patient are brought together, has led (as is alleged) to over-consumption of medical care, to a passion for drugs and so forth? It must be admitted that up to now there have been plenty of generalisations; take, for instance, the generalisations about large numbers of people changing their doctors, on which administrative action was based without, as far as we know, any facts. Little in the way of objective evidence has been published and no basic researches into the actual working of the service have yet been undertaken.

The need for more knowledge and even a modicum of investigation into the working of the service is obvious to anyone who tries his hand at answering the questions put by overseas visitors to our universities and medical schools. We could also deepen our understanding of these problems of demand for medical care by the method of comparative studies applied to societies where the psychology of pain and the fear of death resemble attitudes in this country.

A CALIFORNIAN INVESTIGATION

How helpful such studies might be is illustrated by the publication of the results of a study of the costs of medical care in the San Francisco Bay area undertaken during 1947–48 by the Heller Committee for Research in Social Economics of the University of California.[1]

The purpose of this inquiry was to study the expenditures for health care by a group of moderate income,[2] wage-earning families in a typical urban area of the United States. The families included had incomes which were neither so low as to qualify them for extensive free care nor so high as to enable them to pay very large medical bills without seriously endangering their way of life.

Careful and intelligent use of sampling methods brought into the survey 455 families (containing 1504 persons) in which the chief bread-winners were employed as milk-wagon drivers, grocery clerks, or painters. These groups were chosen because they represented groups of considerable size whose earnings were at about the middle of the income scale in California, and slightly above the middle of the scale for urban areas of the States as a whole. In respect of the size and composition of the families, the ages of its members, the place of birth of the head and his wife, and their educational level, the group studied was strikingly similar to the urban population of the United States. About 90% of the husbands and wives were born in the United States and only 2% were of a race other than white. The most typical family was made up of husband, wife, and one or two children, usually of preschool or school age. Information was collected over a period of one year about all sources and amount of income, the kinds of prepayment or commercial insurance policies providing any type of medical care and their cost, illnesses of each member of the family, and expenditure on all forms of medical and dental care. The chapters and appendices on method, research technique, and definition illustrate how much can be achieved on limited resources by careful preparation and by studying the typical rather than by attempting to survey a complete cross-section of the total population.

EXPENDITURE ON MEDICAL CARE

These 455 families spent nearly $135,000, about $300 per family (equal to about £107 at $2.80 to the £1) for all types of medical and dental care during the year the study was made. This would seem a fantastic sum for families in the middle range of incomes in Britain to spend annually on medical and dental care. Only the present high standard of living of urban families in the United States could support such expenditure. Even so, the amounts spent represented about $7\frac{1}{2}$% of the total income of the group, of which 6% was for medical care and about $1\frac{1}{2}$% for dentistry. While such costs may not be considered a serious burden for families with incomes of about $4000, it must be recognised that it is only a statistical accident if the medical bills of a given family approximate to the average for the group as a whole. This study, like many others in the United States, Canada, and elsewhere, shows the wide variation of medical expenditures. A quarter spent less than $2\frac{1}{2}$% of their incomes; about half spent between $2\frac{1}{2}$ to 10% of their incomes; a fifth spent between 10 to 20%, and about 5% spent more than 20% of their incomes. Thus, a quarter of all the families were seriously crippled during the year by medical and dental bills, even though not a single case

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[1] Cost of Medical Care. By E. H. HUNTINGTON. Berkeley and and Los Angeles: University of California Press. December, 1951. Pp. 146.

[2] The group selected were in occupations where full-time earnings were roughly equivalent to the average for San Francisco production workers in manufacturing—i.e., between $3000 and $4000. The total income of many families was increased by premium rates, overtime, earnings of other persons, &c. The median total income was $300 to $500 higher than census estimates for urban families throughout the United States and $500 to $800 higher than Federal Reserve Board estimates for spending units whose head was a skilled or semiskilled worker.

Prof. PATRICK MEREDITH thought that the application of the Pennsylvania State College project to medical students was of dubious value. It was fashionable to call for such research, but this was not the way that useful results were obtained. The weakness was that the investigator was obsessed with films, whereas the correct approach was by study of the best method of communication. In general he had found[2] that empirical facts and shapes were better communicated by visual methods, whereas knowledge of special words and that derived by inference from facts was best taught orally. In a test he had used four visual methods: a complete film, still pictures, a film and pictures, and short film sequences and pictures. It was only with the last two of these that the visual method proved better than oral teaching, which seemed to indicate that breaking up the medium of instruction facilitated learning. On the whole he was convinced that the film had no advantage over the oral method. "Many films are like the old herbal remedies—doubtful and dangerous."

Discussion arose on the question of emotional as against factual presentation. Dr. JOHN BURTON said that the purely factual film was often as dead as mutton. On the other hand the introduction of an emotional scene to put over a point was bound to fail, since the artificiality was readily appreciated. Professor MEREDITH pointed out that the integrity of a good factual film in itself provided the stimulus to the audience's emotions.

Several speakers referred to the way in which difficulties of organisation prevented the wider use of films. They were often difficult to locate; the previewing of a number of 40-minute films in order to select the best was almost impossible; and the arrangements necessary for projection made the showing of a film a tedious matter. Mr. WHITE, of the Pharmaceutical Society, suggested that the most urgent need was for [illegible] automatic projectors which could be [illegible] lecturer's desk. Dr. P. J. COLLARD appealed for the introduction of the moviola, so that students could view films individually and at their leisure. Several speakers appealed for shorter films. The 40-minute film was of little value in teaching, while short extracts from these films, which would often be useful, were almost impossible to obtain.

The problem of locating films is partly solved by the British Medical Association's catalogue of films in its own library; the British Film Institute's library and catalogue of specialised films; and the Scientific Film Association's catalogue of all medical films available in Great Britain, which is to appear shortly. It is evident, that if films are to be profitably used, medical schools will have to ensure efficient arrangements for projection. All too often films are shown on unserviced projectors by unskilled projectionists; the image is thrown on a dirty wall; and an ill-placed loudspeaker emits a reverberating cacophony. Under these conditions it is not surprising that many teachers ignore the film as a teaching medium.

COMBINED ACTION ON THE "CLOSED SHOP"

Durham County Council has been requested in a letter from the Joint Emergency Committee of the Professions to give an undertaking that its professional employees shall not be subjected to the policy of compulsory membership "in whatever manner, direct or indirect, it may be applied." The committee "reluctantly finds it necessary to impose some time-limit upon further exchanges in this protracted dispute, which has already lasted more than a year." If no satisfactory undertaking has been received by April 30, the committee "will be constrained to take further action to protect an essential principle of professional freedom." The committee expresses willingness to send a deputation if the council should consider that this would serve any useful purpose.

The Joint Emergency Committee of the Professions consists of representatives of the following professional organisations: British Dental Association, British Medical Association, Engineers' Guild, National Union of Teachers, Royal College of Midwives, and Royal College of Nursing. The number of professional workers represented by the committee is about 330,000.

Parliament

Heating Appliances (Fireguards) Bill

ON March 14 Mr. D. G. BULLARD moved the second reading of this Bill which was carried without a division. In the course of the debate several members paid tribute to the work of Dr. and Mrs. Colebrook in collecting much of the evidence on which the Bill is based.

QUESTION TIME

Rural Doctors and the Prescription Charge

Mr. P. A. D. BAKER asked the Minister of Health if he would exempt from the prescription charge rural doctors dispensing their own prescriptions.—Mr. H. F. C. CROOKSHANK replied: It is intended that the charge should be paid by the patient, and it would not be equitable to exempt from the charge such patients as happened to get their medicines from dispensing doctors. I am about to discuss the doctors' difficulties with the British Medical Association.

Articles freed from Price Control

Replying to a question Mr. P. THORNEYCROFT, president of the Board of Trade, said that X-ray plates and films, spectacles and spectacle cases, lorgnettes, pince-nez, monocles and spy glasses, sanitary towels and substitutes therefor, and hand-propelled and mechanically propelled invalid carriages, invalid chairs, and invalid tricycles were among the articles which had been freed from price control by the Board of Trade since the present Government took office. He would watch the position constantly. If there was a need for price control it would be imposed.

Social Survey Reports

Replying to a question Mr. J. A. BOYD-CARPENTER, financial secretary to the Treasury, said that among the subjects investigated by the Social Survey during the last two years were: nutrition of elderly people; education and vocational background and the spare-time activities of adolescents; 'Medresco' hearing-aid; young children's diets; night-baking; road safety; welfare foods; diphtheria immunisation; and incidence of ill health and injuries, as well as the use made of the medical service.

Public Health

Variola Minor In Lancashire

THE outbreak of variola minor in Lancashire remains confined to Rochdale and the adjoining districts. Uncorrected notifications in the five weeks up to that ended March 15 numbered 91, made up as follows: Feb. 16, 1; Feb. 23, 18; March 1, 7; March 8, 62; and March 15, 6. Up to noon on March 18 there was no confirmation that the disease was present elsewhere in the country.

Changes In London's School Health Service

At a meeting on March 5, London County Council education committee agreed that pupils should be weighed and measured only at the four periodic medical examinations—i.e., in the first term at school, in the 7th and 11th years, and in the term before leaving. Hitherto this has been done twice a year. The revised procedure is expected to save the equivalent of 11½ nursing sisters. As an experiment, in three divisions school nursing sisters are to conduct terminal hygiene examinations on the basis of not more than 20 pupils an hour, instead of the present 50 children per hour.

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[2] University of Leeds Institute of Education: Researches and Studies, no. 5. Leeds, 1952.

In England Now

A Running Commentary by Peripatetic Correspondents

LAMENT OF AN EXILE

There is no spring here, only snow and slush. There are no violets, no spinneys and woods, no primroses, no English lanes, no oak trees. They cut their trees down here; the roots are bad for the foundations of their horrid little frame houses. There are no sand dunes, the sea is so far away.

There are no beery pubs, only obsequious funeral [illegible]; no fruit barrow boys, only 'Cellophane'-wrapped fruit in food chain stores: no sawdust on the floors of butcher shops, instead men pick up neat wedges of pale meat from a colossal white freezer.

In England you have high taxes, no luxury, no cigarettes, watery beer, few 'Nylons,' little meat. But you have the Cotswolds, the wet sands of Devon, the low hills of Dorset, and the woods of home.

* * *

St. Vitus Hospital,
London, S.E.5.

Dear Dr. McPhail,

Re McBeth, Lady F. Aet 49.
Dunsinane Castle, Inverness.

There have been some interesting developments in this case of yours, who was admitted here as a V.P. 3/52 ago, with the presenting symptoms of nightmares and somnambulism, and I thought you might like an interim report.

On admission, your patient was very much the gracious lady, and in the interview-situation could beguile the time with registrar and consultant alike. But there was, I felt, beneath this innocently flowery façade a certain ophidian malice. She was, for all that, anxious and depressed, and I was half-inclined to accept your diagnosis of Agitated Depression, precipitated, as I think you suggested, by the recent death at her own house of her husband's chief—guilt-feelings following the loss of a father-figure, I suppose—when, much to my registrar's excitement, she began sleep-walking again. The hand-washing ritual you mentioned was again observed, and a few fragments of speech overheard: "To bed, to bed, to bed . . . put on your nightgown . . . who would have thought the old man to have had so much blood in him?" We followed up this incident with a battery of tests, but the results were rather disappointing. Her E.E.G., 17-ketosteroids, and oxymetry readings were all within the normal range. But the Rorschach gave a very disturbed record. Indeed, at the first bichromatic card she shrieked, wrung her hands, and exclaimed "Out damned spot!"

Soon after this, we showed her at our weekly case-conference. There was the usual dichotomy of opinion on diagnosis between the classical and psycho-analytic schools. I was, I fear, so naïve as to suppose that the words noted in her somnambulistic episode might be mere repetitions of her own speech, made perhaps in some stress-situation. But the Neo-Kleinians had no difficulty in interpreting them, and assured us that they referred to an early sexual trauma. In the end, we agreed so far as to make a diagnosis of "Reactive Depression and Anxiety-Hysteria with Obsessional Features and a strong Schizoid colouring in a woman of the involutionary age-group."

We were all set for the initiation of active treatment within the next fortnight or so—E.C.T., or actively interpretive psychotherapy, I forget which—when the husband appeared and persuaded the patient to hand in her discharge. I would conjecture that he is nearly as disturbed as his wife. After leaving the ward he came up to me and said, confidingly, "Didst see the Weird Sisters?" I reassured him and explained that in all probability they were only nurses. (These West African girls are very good, but paranoids *will* build up a delusional fabric around them.)

The prognosis must be guarded. I have known patients showing this symptom-complex who have died holily in their beds. But there is, I fear, a definite suicidal risk. I trust you will keep me abreast of future developments.

Yours sincerely,

A. BURNHAM-WOODE
Baconian Professor of Psychological Medicine.

A new method of treating black eyes, said to be highly efficacious, is reported from the United States. Instead of the time-honoured lump of beef-steak, a weak galvanic current is applied before the bruise appears. It seems strange that this method should be introduced on the other side of the Atlantic, where large juicy steaks abound. However, the Americans need not fear power-cuts, which might seriously interfere with the treatment over here! Another culinary-medical American invention is a custard-flavoured antibiotic for children with whooping-cough or measles. If this trend continues we shall have to scrap the phrase "Took his medicine like a man," in favour of "Took his punishment like medicine."

* * *

An English girl can grow up without ever seeing a baby suckled at the breast—except in reprints from the National Gallery—until she meets her own firstborn in the unfavourable publicity of a maternity ward. At least Sally will not suffer from that deficiency. Three years old and convalescing after pneumonia, she toddled the length of the ward to peep round the screens where our current feeding-problem was being nursed by his mother. She came away with an expression of awe, and whispered to Sister: "Look! That mummy's giving her baby a drink from her tummy!"

* * *

If there is one sphere in which a man might feel that he is lord of his whim, it would seem to be in gambling. Yet Dr. H. D. Landahl [1] finds that even gamblers run true to type. Using mathematical techniques for exploring the methods of reaction in the central nervous system where choice is involved, Dr. Landahl predicted correctly the choice of a series of 50 gamblers. He divides gamblers into four types. The first is intent on winning, whatever the odds against him; the greater the amount to be won, the more he is willing to risk. This type will buy several tickets in the Irish Sweepstake in the hope of winning a big prize. The second is intelligent and cool, assessing the odds and balancing the risk of losing against the hope of a win. He is a good poker player, ending the year with a profit whatever he may have lost. The third wants the thrill of gambling, caring nothing for the odds or even the amount he wins. The fourth wants to bet only on a sure thing; the odds must be heavily in his favour so that the risk is small; he does not want any thrill out of betting. Just because he always wants a sure thing, this type of man is liable to be taken in by racecourse touts who tell him that a race has been "fixed." That man's freedom of choice in thought and behaviour is illusory has been proved during the past fifty years by the psycho-analysts, applying the concept of psychic determinism to normal and abnormal subjects. But this illusion dies hard, and it is salutary to have it exposed again by a science so respectable as mathematics.

* * *

Reply of an old man on my asking how he felt after his abdomino-perineal resection earlier in the day: "Eh, Doctor, it feels as if bottom's dropped out of everything."

* * *

To squirt with water the human ear
Demands but little acumen,
And it's jolly to make the deaf to hear
By ridding them of cerumen.

One cannot too often perform, of course,
So highly moral an action
Which should unstopper an endless source
Of personal satisfaction!

Nevertheless I feel bound to say
That I shall become unhinged
If any more patients come in today
Wanting their ears syringed.

* * *

News from Hospital.—"They had to froze me as they were afraid the anæsthetic would start me coughing ever so funny feeling conscious but body froze stiff hope to be home next week."

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[1] See *New York Times*, March 9.

Letters to the Editor

THE ETHICS OF LEUCOTOMY

SIR,—Permit me to comment on your annotation of Feb. 23 (to which Dr. Winnicott refers in his letter of March 8) as I feel that it includes a statement which may set off many anxious folk, both lay and medical, in search of a mare's-nest.

It is certain, as you imply, that no-one would desire that a noble conscience and a fine sense of responsibility should be damaged. But when we consider leucotomising a patient, are we in fact likely to interfere with such grand qualities? The neurotic does not merely suffer from an isolated collection of symptoms in one part of the mind, the rest remaining healthy; the mind cannot be diseased in one or two small corners, it is always diseased as a whole. It is unfortunate that textbooks of psychology attempt to explain the mind in spatial terms, dividing it into faculties (e.g., cognitive, affective, conative) or in some other manner (e.g., id, ego, super-ego), and often supply diagrams to illustrate such unnatural sectioning. This may give some people the impression that one "part" of the mind can be diseased, whilst the rest remains healthy. This of course is not so—the mind always functions as a whole.

A neurotic, apart from his symptoms, suffers also from a faulty character and personality; which implies, amongst other things, an unhealthy conscience and an unhealthy sense of responsibility. This is confirmed by the descriptions we receive from the relatives and friends of neurotics and from the doctors who look after them. We are informed that they appear to be lazy or obstinate, fussy and over-conscientious, egocentric or self-willed, unduly concerned with their bodily and mental functions at the expense of considering the interests of their relatives and society, or unable to make responsible decisions.

Here is an obsessional woman who keeps her husband awake till 4 in the morning by repeatedly washing and rewashing linen and crockery; there is a hysterical woman who compels her sister to give up work so that she herself can be waited on hand and foot all day. Here is an obsessional man who has been unemployed for 17 years and has lived parasitically on his wife's earnings. There is a hysterical woman who nearly drives her husband crazy by her violent temper tantrums and aggressive violence. Here is a man who works up emotional storms demanding repeated assurances of love from his wife. There is a woman who behaves in a like manner. And so forth. What extraordinary consciences and senses of responsibility such patients must have! If we care to use technical jargon, we might talk of harsh or weak super-egos, fantastic ego-ideals, narcissism, perfectionism, infantile fixations, sadism or masochism in relation to relatives, &c.; but it all amounts to the same from the practical point of view. Why then this anxiety of damaging valuable qualities of the mind? Such anxiety should be expressed only when a healthy mind is being leucotomised, but this occurs only in the tiny proportion of patients operated on for agonising pain—cases where the patient is probably doomed to die of carcinoma within a few months. The alternative for such sufferers is morphine addiction.

Finally, lest I be misunderstood, may I make two points clear. Firstly, I do not mean to pass any moral censure on the neurotic—he behaves as he does because he is impelled by forces of which he is unaware and which are beyond his control. Secondly, I still maintain, as I always have done, that neurotics should receive intensive and prolonged psychotherapy (under which I include changes of environment and employment) before leucotomy is considered. But where all this has been done for several years and the neurotic still remains a burden to himself, to his relatives, and to society, and of course continues to be possessed by an unhealthy conscience and an unhealthy sense of responsibility, then rostral leucotomy should be justifiably considered for those types (e.g. obsessionals) in whom experience has shown that the operation can be successful in a large majority of cases.

Park Prewett Hospital,
Basingstoke, Hampshire.

I. ATKIN
Physician-Superintendent.

DIPHTHERIA CARRIER INVESTIGATION

SIR,—Last week's report by Dr. Bradshaw and his colleagues is of great interest, and provides further evidence that the fear that diphtheria immunisation may increase the carrier-rate in the population, and thereby produce a greater risk of diphtheria in the uninoculated, has been greatly exaggerated. All evidence indicates that in the general population the carrier-rate is reduced together with diphtheria morbidity as a result of immunisation.

The statistical relationship between the decrease in the incidence of carriers and that of clinical cases was clearly demonstrated by studies in Baltimore.[1] Surveys carried out in London school-children in 1942 and 1943 showed low carrier-rates to be present even before diphtheria incidence had reached its present low level.[2] The suggestion that immunisation might increase carrier-rates was based largely upon experience in residential establishments,[3] and this has apparently little relevance to events in the general population.

County Hall,
London, S.E.1.

IAN TAYLOR.

THE UNESTABLISHED PRACTITIONER

SIR,—The profession is now fully aware that the problems of the unestablished practitioner have greatly increased since the introduction of the National Health Service. The British Medical Association has consistently refused to support any betterment of the conditions of assistants or to help the small-list doctor; it has never brought forward or supported any plan to encourage practitioners with large lists to take partners.

This negative policy led to the formation of the Unestablished Practitioners' Group just over a year ago. As yet the B.M.A. has refused to recognise this group and claims to represent "adequately" the unestablished practitioner. The correspondence columns of the medical journals, and the fact that this group already represents nearly 500 doctors, invalidate this claim.

Until the problems involved are recognised by the B.M.A. and plans put forward for their alleviation, the Unestablished Practitioners Group will strive to implement its policy, which in brief is as follows:

1. To press for alterations in the N.H.S., particularly in the method of remunerating general practitioners, so as to increase the number of established principals, primarily by encouraging partnership rather than assistantship, and also by helping the bona fide "squatter."
2. To render unprofitable the commercialised permanent assistantship system, by not allowing a principal who employs an assistant any increase above the agreed maximum list permitted to an unassisted practitioner.
3. To press for removal of restrictions on change of doctor.
4. To modify the "trainee general practitioner" scheme so that the trainee would be employed not by the principal but by the executive council, who would pay the trainee's salary, be responsible for his conditions of work, and arbitrate in any dispute.

The terms of reference of the working party set up by the Ministry are "to secure a more equitable distribution of the central pool, to discourage unduly large

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1. Frost, W. H., et al. *Amer. J. Hyg.* 1936, 24, 568.
2. London County Council. *Lancet*, 1947, i, 668.
3. Dudley, S. F., May, P. M., O'Flynn, J. A. *Spec. Rep. Ser. med. Res. Coun., Lond.* no. 159. H.M. Stationery Office, 1934.

ists. . . .” These are the very matters which affect the unestablished doctor most. But there is not one assistant or unestablished practitioner on this working party! One is justified in asking whether this is because the B.M.A. “adequately represents” the unestablished practitioner, or whether it has merely forgotten this growing minority which is already on a full-time salaried service imposed by the profession itself. It should be remembered that the existence of a large number of unestablished practitioners is a threat to the prestige of the profession as a whole.

The unestablished practitioners have a just case and will succeed if they act through their own organisation—the U.P.G. We therefore ask all doctors seeking entry into general practice, all assistants, and small-lists practitioners who have not already joined, to apply for membership of this group.

39, The Avenue,
London, N.W.6.

L. RUSSELL
Chairman,
Unestablished Practitioners Group.

MERCURY AND PINK DISEASE

SIR,—The interesting paper by Dr. Holzel and Dr. James (March 1) certainly suggests that mercury is an ætiological factor in acrodynia.

I have under my care a baby boy, aged 9 months, with typical pink disease who has regularly been given two teething powders a week for 5 months, and additional powders when he was restless and fretful. A 24-hour specimen of his urine yielded 70 µg. of mercury per 100 ml.—a very much higher value than the normal. The baby has been treated with dimercaprol with a satisfactory result.

Even if mercury were found to have no bearing on the causation of acrodynia, its administration to babies in the form of teething, cooling, or soothing powders should be stopped. These powders are advertised to the public, and their main recommendation appears to be that they have been in use for over a hundred years. They therefore became popular at a time when purging and blood-letting were regularly used in the treatment of many diseases. Since then medicine has changed, and the treatment of fretful, hot, and teething babies has advanced.

These powders weigh gr. 2·4–2·8 and contain 27–29% of calomel. There is no justification to give gr. $^1/_2$ of calomel to any baby.

Wanstead Hospital,
London, E.11.

ERIC FRANKEL.

THE ANATOMY ACT

SIR,—It is pleasing to read in your issue of March 8 the letter from the president of the Royal College of Surgeons commending the action taken in Parliament to alter the law, in order to authorise the establishment of eye banks in connection with corneal graft surgery.

For some time now we have been aware of the legal difficulties confronting ophthalmic surgeons in the matter of collecting and storing donated material, and their dependence upon pathological eyes taken from living subjects. The provisions of the Anatomy Act place serious obstacles in the way of collecting material from persons who have just died; and I understand that unless the material is collected within a short time of death it is valueless for use in ophthalmic surgery.

There are other banks that have been established in this country of which the legality is seriously in doubt, owing to the impact of the old Anatomy Act on the procedure followed to collect and store material for ready use in the treatment of bone and other conditions. It is not unlikely that the demand will arise in the early future for the collection and storage of soft tissues—e.g., fascia, arteries, and veins.

The Anatomy Act was originally designed to meet a special set of circumstances arising from the activities of the “resurrectionists.” Perhaps we can safely say that their re-emergence is highly improbable and that the law should be suitably amended to permit of surgeons and pathologists collecting material for the treatment of people who are blind, or otherwise disabled, for research, and for tuition in medical schools. The time appears to be appropriate not only for a minor change in the law but for a review of the Anatomy Act as a whole, to eliminate its restrictions on treatment and pathological investigation and to amend the provisions which may hinder surgical progress.

Medical Defence Union,
Tavistock House South,
Tavistock Square, London, W.C.1.

ROBERT FORBES
Secretary.

TRAINING OF DEAF CHILDREN

SIR,—The letter from Miss Edith Whetnall in your issue of Feb. 23, and the reference to my wife and me in your leading article on the same date, encourages me to hope that you may wish to publish a brief summary of an extensive investigation into the problems involved.

Since 1942, 893 children under five years of age have been referred to the research unit, Department of Education of the Deaf, University of Manchester, for tests of hearing and educational guidance, by otologists, pædiatricians, school medical officers, and other doctors. Of this total 553 children were found to be deaf or partially deaf. The techniques employed in testing their hearing were based on an investigation of the ordinary child's response to sound, from birth to five years.[1] My wife's discovery that informal home training can enable deaf children under two years of age to begin to understand speech through lip-reading was demonstrated, to a large audience of teachers of the deaf, four years later. The youngest child who took part was one year and three weeks old. Her parents had given her training, under my wife's guidance, for five weeks. She was one of more than 30 deaf children, whose ages ranged from twelve weeks to nearly three years, who had had similar training during the preceding twelve months.

In 1948 financial support from the Medical Research Council and the Leverhulme Trust made it possible to extend the scope of this investigation. Two workers were appointed—Miss D. M. Gutteridge, as a research fellow to study the provision of guidance to parents, and Mr. D. C. Kendall, a psychologist, to investigate methods of assessing the mental abilities and linguistic and social development of young deaf children.

To follow up the histories of the children who have had home training is a main aim of the research. Many are now pupils in schools for the deaf, from which reports have come referring to their natural and unforced habits of lip-reading, markedly social attitudes, and constant spontaneous attempts to talk, sometimes in phrases.

Of all the children followed up, only one who is profoundly deaf has been able to gain her education in an ordinary school. She competes successfully with other pupils of her own age in general school subjects. Her mother, on learning that she was deaf, took a full course of training and became a qualified teacher of the deaf.

Some of the partially deaf children, with the help of hearing-aids and lip-reading, and after home training by their parents and special educational treatment by qualified teachers of the deaf, have become capable of successful attendance at ordinary schools. For others, education in classes or schools for the partially deaf has proved to be necessary.

Of the children found severely or totally deaf to speech, a large majority are now pupils in schools for the deaf, and, in the cases which we have been able to follow up, their educational achievement and social competence is of a higher standard than is usual among deaf children who have had no early training. Our evidence is that deaf children, besides home training, need full-time special educational treatment in a recognised day or residential school for the deaf, or a private school for the deaf.

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[1] Ewing, I. R., Ewing, A. W. G. *J. Laryngol. Otol.* 1944, 59, 309.

A few are being taught at home by qualified teachers of the deaf. However early special training and education have been begun, an intelligible standard of speech has proved possible for profoundly deaf children only through the help of fully qualified teachers of the deaf over a period of years.

All who are in any way responsible for this investigation wish to take this opportunity of expressing gratitude for continued collaboration by so many members of the medical profession, and in particular by the chief education officers and school medical officers who are helping us at the present time to follow up the subsequent histories of all children with defective hearing within their areas.

Department of Education of the Deaf,
University of Manchester.
A. W. G. EWING.

ADRENOCORTICOMIMETIC EFFECTS OF ANTIBIOTICS

SIR,—Since you published my paper[1] mentioning the "profound adrenocorticomimetic effects" of streptomyces-derived antibiotics, I have been asked by private correspondents to explain, first, what I meant by an adrenocorticomimetic effect, and secondly why, if such effects exist, nobody else has drawn attention to them. In reply to the second half of the question I can only remark that the salicylates, also, were widely used for many years before anyone pointed to the resemblance between their effects and those of adrenal cortical extract.[2]

The data in the accompanying table have been compiled over the past two years from three separate clinical pathology services. Some of the diseases listed under Therapeutic Efficacy do not respond satisfactorily to any form of treatment, and their presence under this heading does not imply that I would recommend either form of therapy: they are placed there merely because, in the opinion of the attending physicians, some benefit was observed during treatment. Among the remaining 19 effects listed in the table are those occasional ones which reflect a tendency towards correction of an abnormality—e.g., either antibiotics or A.C.T.H. may reduce the erythrocyte-sedimentation rate (E.S.R.) in acute leukæmia or rheumatic fever but they will not reduce the already depressed E.S.R. of bronchial asthma. (A normalising effect such as this is reminiscent of that seen with "alterative" remedies; salicylate or cinchona will regularly lower the temperature of the fevered but leave the normal temperature unaffected.) In many instances, however, untoward adrenocorticomimetic actions, particularly those tending to create electrolyte imbalance, have been the covert cause of failure to respond to streptomyces-derived antibiotics. The reason why viomycin (from *Streptomyces violaceans*) was never generally released was that severe derangements in electrolyte balance, all in the direction of hyperadrenocorticism, were observed in tuberculous patients receiving the antibiotic.[3] The presumption that the other streptomyces-derived antibiotics are devoid of this effect appears to be quite unfounded.

Heart-failure due to natræmia and hypokalæmia may rarely cause death in the usual mild or moderate infection treated with antibiotics, but may be commoner when the infection is severe. If this thesis is proved it will help to explain how a group of chemical substances, such as the antibiotics or salicylates or arsenicals, which are structurally unrelated to either the corticosteroids or the corticotropins, may nevertheless duplicate the physiological and pharmacological action of the latter. It seems that the corticomimetic response *is obtained only in the* seriously ill—i.e., in those who have shown a decomp satory reaction to stress. In such patients the adren corticotropic mechanism is not meeting the stre situation; if it were, there would be no adaptati disease or syndrome.

It has recently been postulated that in such reacto there is a "block" in the humoral reflex arc who normal integrity furnishes the stress-compensator mechanism of adrenocorticoid elaboration.[4] *Removal o* this "block," in face of a profound stress stimulus, followed by an overwhelming effusion of adrenocortic hormones. The block is evidently in the component o the humoral reflex arc proximal to the anterior pituitar

EFFECTS OF STREPTOMYCES-DERIVED ANTIBIOTICS AND CORTICOTHERAPEUTIC AGENTS

Effect	Streptomyces-derived antibiotic					Cortico-therapeutic agent		
	Streptomyces griseus residue †	Streptomycin salts	Aureomycin	Terramycin	Chloromycetin	Adrenal cortical extract	Cortisone	Pituitary adreno-
Therapeutic efficacy* in:								
acute leukæmia ..	x		x	x	x	x	x	x
"hæmolytic" anæmia	x			x		x		
infantile erythroblastosis	x						x	
"rheumatoid" arthritis	x	x		x	x		x	x
thrombopenic purpura		x		x		x		
agranulocytosis ..	x							x
"atypical" pneumonia	x	x	x	x	x	x	x	
bronchial asthma ..	x			x		x	x	
pollinosis				x		x		
necrotising hepatopathy ("viral" hepatitis)	x	x		x		x		x
lupus erythematosus ..		x		x			x	
polyarteritis nodosa ..	x	x		x			x	x
pemphigus	x			x	x	x		x
scleroderma	x						x	
plasmocytic myeloma	x		x			x		x
dermatomyositis ..				x			x	
demyelinating neuropathy	x			x		x		x
atopic dermatoses ..	x			x			x	x
nephrotic syndrome ..	x		x	x		x		
uveosis	x			x		x	x	
Reiter's syndrome ..				x	x		x	
disseminated herpes (Kaposi)	x						x	
benign lymphoses ("infectious mononucleosis")	x	x	x	x	x	x	x	x
Hodgkin's lymphoma	x			x				x
leucosarcoma	x					x		
Plasma-albumin synthesis (restoration of A/G ratio)	x	x		x	x	x		x
Depression, abnormal E.S.R.	x		x	x	x	x	x	x
Delayed wound healing ..		x		x	x		x	
Sodium and water retention	x	x	x	x	x	x	x	x
Potassium depletion ..		x		x	x	x	x	x
Eosinopenia ..	x	x	x	x			x	x
	x	x		x		x	x	x
effect)	x			x	x	x	x	x
Diminished plasma polyphenols	x			x	x		x	
Hyperglycæmia	x	x		x	x		x	x
Acneiform eruption ..	x						x	x
Cutaneous flush	x						x	x
Diminished plasma-iron				x			x	
Rise of erythrocyte-esterase	x		x	x		x		x
Lipæmia	x	x		x	x		x	x
Diminished urobilinuria			x	x			x	
Augmented blood coagulability	x			x			x	
Hypertrichosis (in females and prepuberty) ..	x	x					x	

* Frequently transient or minimal.
† Now known to contain, in addition to streptomycin and vitami B₁₂, a certain amount of folinic acid ("citrovorum factor" and steroid material.
x = positive effect observed.

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[1] *Lancet*, 1951, i, 1157.
[2] Cochran, J. B., Watson, R. D., Reid, J. *Brit. med. J.* 1950, ii, 1411.
[3] Werner, C. A., Tompsett, R., Muschenheim, C., McDermott, W. *Amer. Rev. Tuberc.* 1950, 63, 49.
[4] *Int. Rec. Med.* 1951, 164, 117.

r there is a response to injected adrenocorticotropin. However, in those who are ill and who have presumably ailed to make an autochthonous adrenocorticotropic esponse, it is found that eosinopenia is still not produced y an "alarm" agent such as adrenaline.[5] This last fact ndicates the location of the block; but the way in which ntibiotic therapy removes it remains to be elucidated.

Laurelton, Long Island,
N.Y., U.S.A.

ROBERT D. BARNARD.

PROCAINE PENICILLIN AND BREATHING EXERCISES IN POSTOPERATIVE PULMONARY COMPLICATIONS

SIR,—We should like to draw the attention of Mr. Daintree Johnson (March 8) to the fact that our series ncluded a control group. The incidence of chest complications in this group was 12%, compared with 15% or group 1 (penicillin only), 18% for group 2 (penicillin nd breathing exercises), and 20% for group 3 (breathing xercises only), although we showed that there was a satisfactory distribution of high risk cases throughout he groups. The incidence of chest complications was owest in the control group. If Mr. Johnson wishes to say that these figures could support his hypothesis that penicillin and breathing exercises could reduce the ncidence by 30%, by similar reasoning the treatments ould have increased the incidence of the complications by a much larger percentage.

Our conclusion in the summary that "procaine penicillin and breathing exercises before and after operation id not significantly reduce the incidence of postoperative pulmonary complications in 160 cases of inguinal hernia" s a re-statement of the results of the experiment.

Department of Medicine,
Middlesex Hospital,
London, W.1.

K. N. V. PALMER
B. A. SELLICK.

PRISCOL IN OBSTETRICS

SIR,—It is almost twelve months since Dr. P. A. Foster suggested in your columns[6] that 'Priscol' might be of value in obstetrics. This vasodilator was alleged to have oxytoxic effects that might be used in the induction of labour and the treatment of uterine inertia; it was also considered to be of use in cases of toxæmia, and to enhance the action of analgesic drugs in labour. As we have seen no further report on this subject, a brief record of our experience may be of interest.

Priscol was given to 8 patients in an attempt to induce labour. The group contained only 2 primigravidæ, and all had reached at least the 38th week of pregnancy. The indications for induction were postmaturity (5 cases), antepartum hæmorrhage, obstetric history, and toxæmia. The usual dosage of the drug was one intramuscular injection of 25 mg., repeated twice if necessary. 2 patients were given one or more doses by mouth, and on one occasion the third dose by injection was increased to 50 mg. In all, fourteen injections and four oral doses were administered. There was no evidence of any ill effect on mother or baby, although a few patients noted sensations of warmth and tingling of the extremities. One baby was subsequently stillborn following antepartum hæmorrhage.

The results were difficult to evaluate as other methods of induction were often in use concurrently. In 5 of the cases a high puncture of the membranes had already been performed, and 2 patients had received pitocin injections. However, on 3 occasions the initial injection of priscol produced a prompt response with the onset of regular uterine contractions lasting 30–60 seconds and occurring every 4–7 minutes. 2 of these patients failed to start in labour and the contractions passed off, but with the 3rd it appeared that the onset of labour coincided with the contractions induced by priscol. In 3 other cases there was no uterine response whatever to repeated doses of priscol. On one occasion there was a limited response to the final dose, and in the remaining patient contractions were induced by the first injection but could not subsequently be reproduced.

Priscol was used in 2 cases of late pregnancy toxæmia, each of which was probably superadded to essential hypertension. In the 1st patient, a multipara at 39 weeks, an initial injection was followed by oral medication with 25 mg. thrice daily for 5 days. After an initial fall, the blood-pressure increased gradually during treatment and fell slightly at its conclusion. In the other patient two doses of priscol 25 mg. appeared to increase the diastolic pressure, and no further injections were given.

As a result of these observations it is our opinion that under favourable circumstances priscol may produce contraction of the gravid uterus at term. In the dosage used we did not succeed with the induction of labour, but it may be that better results can be obtained with the use of the intravenous-drip technique.

J. B. FARQUHAR

Birmingham.

W. G. MILLS.

GASTRIC DILATATION IN POLIOMYELITIS

SIR,—I was very interested to read Dr. Westlake's letter (Feb. 16). It has been realised for a good many years that the most exact management of a respirator case would involve several arterial punctures and the use of apparatus which is unavailable in most hospitals even in the heart of London. We must therefore devise a method whereby exactness is sacrificed to a small extent for the sake of simplicity. Spirometry seems to me to be the answer.

In my opinion biochemical estimations are too slow for routine use. In order to study alkalæmia or acidæmia in respirator cases, estimation of alkali reserve naturally suggests itself; but I agree that it is not a great help in the management of patients with respiratory paralysis. However, numerous clinical observations have shown that the alkali reserve in a patient who is breathing comfortably in a respirator is within normal limits, but if this mechanical aid is withdrawn for a few hours there is a slight fall in the alkali reserve. In explaining this one must remember that prolonged paralysis of respiratory muscles, recumbency, and various other factors cause changes in the lungs themselves and probably in the kidneys.

K. K. HUSSAIN.

ACUTE INFECTIONS OF THE FINGERS AND HAND

SIR,—Mr. David Bailey's article (Jan. 26) and the ensuing correspondence are very stimulating. Mr. Clarkson (Feb. 16) summarised the issue by saying that the problem of treatment can be divided into: (1) overcoming the infection; and (2) getting rid of dead tissue.

Using Mr. Bailey's classification, with web-space infection and paronychia usually only the first of these problems is present. At the General Infirmary at Leeds, by observing the principles that I have already described,[1] a well-placed incision with evacuation of all pus leads to complete healing and return to work in four days in 95% of cases. With pulp-space infection and subcutaneous abscesses the second of these problems is usually present. At Leeds we have been trying for some time to assess at operation the "state" of the lesion.

Grade I consists of the relatively early case, in which there is no skin necrosis or tissue destruction (as judged by absence of slough), and only a small cavity is present. The time of healing of these cases should approximate to that of web-space infections.

Grade II consists of those in which there is a small skin loss, with considerable tissue destruction as shown by a large amount of slough and/or an appreciable residual cavity. In these cases even when the infection is overcome the slough must be evacuated sooner or later and this cavity obliterated, either by collapse, suturing, or filling with granulation tissue. In manual workers the thick skin prevents collapse and obliteration of the cavity.

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[5] Brenner, L. O., Waife, S. O., Wohl, M. G. *J. Lab. clin. Med.*, 1951, 37, 593.

[6] *Lancet*, 1951, i, 802.

[1] *Lancet*, 1951, i, 1038.

Grade III are those in which there is extensive skin loss (usually found in subcutaneous abscesses) and tissue loss. Even when infection is overcome the skin loss must be replaced and in the absence of grafting the treatment is now that of an epithelialising ulcer and not a septic finger.

Grade IV—relatively rare with us—all the above lesions plus bone necrosis.

The healing-time of all these grades can be expected to be *quite different; and I suggest that if surgeons* were to agree on this or some other practical form of grading, comparison would be much more useful.

As a result of our attempts at grading we have now got some idea of the factors that convert the optimum grade I into other grades:

1. Prolonged use of heat applications with the hope of either aborting the *infection or making it point quickly.* It is possible that the former may sometimes be achieved, but I suggest that if no marked improvement has occurred *within 24 hours further radical measures are necessary.* Factory nurses and ambulance-men should have this impressed upon them.

2. Prolonged use of penicillin by practitioners in the hope of aborting established abscess formation or preventing spread *whilst waiting for the abscess to point.*

3. Inadequate previous operation. We constantly see cases in grades II and III where a minimal incision has been used, *without the rest of the careful surgery advocated by* Mr. Bailey.

Observations at other clinics may show other preventable factors in the advanced grades.

As Professor Pilcher points out (Feb. 23), the teaching hospitals bear some of the responsibility in allowing grades II, III, and IV to be too often present, when the cases come to *hospital; and I trust that* Mr. Bailey's most stimulating paper will sustain interest in the treatment of this condition.

Leeds. MAURICE ELLIS.

AGGLUTINATION TESTS FOR RHEUMATOID ARTHRITIS

SIR,—*In your issue of Feb. 23* Dr. Hobson *and* Dr. Gorrill present evidence which is held to show that the agglutinating factor in the serum of patients with rheumatoid arthritis is closely associated, if not identical, with the fraction of complement known as C_4.

I believe that Meyer[1] was the first to suggest that the factor in human serum which agglutinates sensitised sheep cells might be a heat-stable fraction of complement (C_3); C_4 was not then known. From experiments with zymin-treated sera I would agree with Hobson and Gorrill that the agglutinating factor is distinct from C_3, since it is possible to destroy completely the lytic action *of rheumatoid sera by treatment with zymin and at the* same time to leave the agglutinating factor unaffected. Exactly the same result was obtained, however, with serum treated with ammonium hydroxide, provided the concentration of the reagent was sufficiently low. *Following the technique of Gordon et al.*[2] *it was found* that the lytic activity of 1·0 ml. of rheumatoid serum was completely destroyed by 0·25 ml. of $\frac{N}{6\cdot5}$ ammonium hydroxide, whereas its agglutinin titre remained unaffected. If, on the other hand, the amount of ammonium hydroxide was increased, as in the experiment of Hobson and Gorrill, both agglutinative and lytic actions were affected.

Rose et al.[3] showed that the agglutinating factor in rheumatoid serum was contained largely in the electrophoretically separated $\beta\gamma$ globulin fraction. Most of the agglutinating activity is contained in the precipitate obtained with ammonium sulphate at a *concentration of* 1·30 mol. per litre, the remainder being found in the precipitate obtained at 1·64 mol. per litre.[4] But according to Pillemer et al.[5] C_4 is largely contained in the fraction obtained at a concentration of 2·2 mol. per litre; in our hands, fractions obtained at concentrations above 1·64 mol. per litre contain no agglutinating activity.

According to Pillemer et al.[6] specific *aggregates* invariably adsorb C_4 from fresh unheated serum but not from heated serum. I have repeatedly observed that adsorption of rheumatoid serum on washed sensitised sheep cells leads to only partial loss of agglutinating *activity, and this reduction in titre is* the same whether heated serum or fresh unheated serum is used. These observations do not exclude the existence of some relationship between the agglutinating factor and C_4; they do, however, suggest that the two components are distinct.

The technique of the test used by Hobson and Gorrill is similar to that described by various workers[7,8] in that it is based on the titration of serum from which heterophil antibody has been adsorbed. Using the test described in 1950 I find[9] that 67·2% of 61 inpatients (taken as being comparable with Hobson and Gorrill's *rheumatoid cases) were positive as against 85·0% in* their sample. The difference is 17·8±7·4%. On the other hand, as against the 13·2% false positives in 6 control cases reported by Hobson and Gorrill, I have found 2·5% false positives among 1301 control cases. The difference is 10·7±4·1%, which is significant in the direction opposite to that shown for the rheumatoid *cases. Thus, in so far as the comparison* is justified, increased sensitivity is apparently associated with some loss of specificity.

From tests at three levels of sensitivity of some hundreds of rheumatoids and control cases it was shown[4] *that the sensitivity of the modified agglutination* test could only be increased at the cost of a loss in specificity; and the experiment reported by Hobson and Gorrill (their table III) confirms this finding. As regards the agglutinating factor there is clearly some overlap between patients with *rheumatoid arthritis,* patients *with other* diseases, and normals. The choice of sensitivity level is all-important, for if the test is to be of clinical value negative results should be found particularly in those conditions which, though often difficult to distinguish clinically from rheumatoid arthritis, require different treatment. In a recent analysis[9] it was shown that all of 30 cases of ankylosing spondylitis, in which active arthritis of joints peripheral to the hips and shoulders was a complicating feature, were negative (see Hobson and Gorrill's finding in two apparently similar cases[3]); with very rare exceptions all cases of osteo-arthritis, *including many examples of the generalised type,* which according to Kellgren and Moore[10] may be confused with rheumatoid arthritis, were also negative, as were all cases of undoubted gout and cases of bacterial arthritis of various types. When, however, the sensitivity level was *increased, positive* results occurred in some of the above-mentioned non-rheumatoid syndromes. The sensitivity level used in these studies was defined in terms of the agglutinin titre of an arbitrary human serum, thus enabling the sensitivity to be maintained at a "standard" *level over long periods and with different* batches of cells and amboceptor.

With a test based on the titration of serum from which heterophil antibody had been adsorbed, Dr. Scott, whose paper also appears in your issue of Feb. 23, seems to have obtained very low specificity and only moderate sensitivity; perhaps the critical titre was set too low. The low specificity certainly contrasts strongly with the experience of others[7] [8] using this type of test, and considerably reduces the significance of the experiment in which the Rose test and the modified method are compared.

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[1] Meyer, K. *Z. ImmunForsch.* 1922, **34**, 229.

[2] Gordon, J., Whitehead, H. R., Wormall, A. *Biochem. J.* 1926, **20**, 1028.

[3] Rose, H. M., Ragan, L., Pearce, E., Lipman, M. O. *Proc. Soc. exp. Biol., N.Y.* 1948, **68**, 1.

[4] Ball, J. Thesis for Doctorate of Medicine in the University of Manchester, 1951.

[5] Pillemer, L., Ecker, E. E., Oncley, J. L., Cohen, E. J. *J. exp. Med.* 1941, **74**, 297.

[6] Pillemer, L., Seifter, S., Ecker, E. E. *Ibid*, 1942, **75**, 121.

[7] Ball, J. *Lancet*, 1950, ii, 520.

[8] Heller, G., Jacobson, A. S., Kolodny, M. H. *Proc. Soc. exp. Biol., N.Y.* 1949, **72**, 316.

[9] Ball, J. *Ann. rheumat. Dis.* (In the press).

[10] Kellgren, J. H., Moore, R. *Brit. med. J.* Jan. 26, 1952, p. 181.

In rheumatic diseases diagnostic criteria vary from place to place. Moreover, the proportion of "rheumatoid" cases giving positive results in the agglutination test is influenced considerably by various clinical features, some of which may easily be assessed differently by different observers.[9] It is therefore important to base one's conclusions on studies of fairly large samples of both rheumatoid and control cases. For the same reasons detailed comparisons of the results of various investigators are not very helpful. From studies of over two thousand cases it was concluded [9] that the modified test can be of practical value to the clinical rheumatologist, and can also serve as a useful reference point for the comparative study of the various rheumatic syndromes.

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University of Manchester.

J. BALL.

RHESUS NOMENCLATURE

SIR,—While agreeing with Dr. Wiener (Feb. 2) that a CDE-cde phenotype (Rh-Hr blood-group) notation is desirable for specialists, I am convinced that there exists a more substantial general need—for a CDE (Rh) phenotype notation as succinct as AB-A-B-O. The obvious method is to apply Fisher's[1] CDE nomenclature to Wiener's[2] Rh phenotypes, as is shown in table I.

Fisher's notation is based on his theory that the Rh-Hr unit of inheritance is a combination of one or other member of each of three separate pairs of genes, which he named Cc, Dd, and Ee. Thus, the possible combinations of C or c, D or d, and E or e being eight, the Rh-Hr genetic unit may be any one of eight "triple" genes (see table II). As each individual inherits a triple Rh-Hr gene from either parent, and as eight different things can be paired in thirty-six ways, there are thirty-six Rh-Hr genotypes—e.g., cDE.cde.

The six elementary genes of Fisher's theory—C, D, E and c, d, e—are serologically manifest as agglutinogens, whose corresponding agglutinins distinguish twenty-seven Rh-Hr phenotypes or blood-groups—e.g., DEcde. Further, these various agglutinogens may be found, under certain conditions, to act as antigens; and in the case of C, D, and E—especially D—this happens commonly. But so very rarely are c, d, and e antigenic that they can safely be excluded from phenotypic considerations, as is the feeble antigen O in the case of the blood-groups AO and BO, and as are also the Hr antigens themselves (see table III) in the case of the phenotype "Rh-positive."

TABLE I—THE Rh (CDE) PHENOTYPES.

Notation used by Wiener	Rh_1Rh_2	Rh_1	Rh_2	Rh_0	rh'rh''	rh'	rh''	rh
Notation based on Fisher	CDE	CD	DE	D	CE	C	E	X

TABLE II—THE Rh-Hr (CDE-cde) GENES

Notation used by Wiener ..	R^z	R^1	R^2	R^0	r^y	r'	r''	r
Notation used by Fisher ..	CDE	CDe	cDE	cDe	CdE	Cde	cdE	cde

TABLE III—THE Rh AND Hr (CDE AND cde) ANTIGENS

Notation used by Wiener	rh'	Rh_0	rh''	hr'	Hr_0	hr''
Notation used by Fisher	C	D	E	c	d	e

But exclusion of c, d, and e would not be justified only on principle: it would also be highly expedient. Outside the specialist laboratories the use of twenty-seven phenotypes would do little or nothing to clarify the subject; whereas the problem would certainly be simplified by a phenotype notation which took account of the reactions of only anti-C, anti-D, and anti-E, using some extraneous letter (e.g., X) to indicate total absence of C, D, and E. Nor is there much prospect that c, d, and e will ever produce sufficient antiserum for use in routine grouping.

Furthermore, anti-C, anti-D, and anti-E do not only suffice for routine phenotyping: they also determine the genotype of the offspring of a known true Rh-negative (cde.cde) mother. In such a family additional use of anti-c and (ideally) anti-d and anti-e may be required to establish the genotype of the father, and so to determine whether or not he is heterozygous; but even so all six of the Rh-Hr antisera together cannot distinguish the alternatives in one group of four different genotypes, and in six other pairs of genotypes: here one can only assume the presence of the most (or more) frequent genotype.

Theoretically, the group of four indistinguishable genotypes are trebly heterozygous—that is, their two inherited units differ in all three component parts (e.g., CDe.cdE)—and the six pairs of indistinguishables are doubly heterozygous (e.g., CDe.cde), while the distinguishable genotypes consist of twelve single heterozygotes (e.g., CDe.CDe) and eight homozygotes (e.g., CDe.CDe). In clinical practice, however, an Rh heterozygote is almost invariably a person with one or more of C, D, and E represented in one of his triple Rh-Hr genes, and with only c, d, and e in the other.

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Blood Transfusion Service,
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T. M. ALLAN.

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[1] Fisher, R. A. Cited by Race, R. R. *Nature, Lond.* 1944, 153, 771.

[2] Wiener, A. S. *Science*, 1943, 98, 182.

HICCUP DURING ANÆSTHESIA

SIR,—I, too, have often seen, in the past, spasmodic movements of the diaphragm unrelated to the respiratory rhythm. In my experience this has been commonest under the following circumstances: (1) with very light general narcosis; (2) during manipulations in the upper abdomen; (3) in the presence of a cuffed tube either in the trachea or in the œsophagus; and (4) in the presence of considerable over-ventilation.

I have not found that hiccup occurs if the alveolar carbon dioxide is kept within normal limits. I have also been able, by adding carbon dioxide, to stop a hiccup when it first begins, but well-established hiccup has proved very resistant. I have not seen hiccup at all during the last three years, when I have been careful not to over-ventilate the curarised patient.

I have found that over-ventilating an anæsthetised and curarised patient reduces very considerably the oxygen uptake, although the stimulus of the operation may keep the respirations going. I have further found, in myself, that deliberate over-ventilation causes distinct analgesia, which is greatly reduced by continuing over-ventilation with oxygen, even to the point of tetany. It would seem possible that the apparently unphysiological action of the diaphragm in the presence of a lowered carbon dioxide tension may be due to local stimulus and tissue anoxia, caused partly by the Bohr effect and partly by the slowing of the circulation that occurs under these circumstances. This seems to be difficult to prove; for anoxia producing the same degree of analgesia as was produced by over-ventilation gave rise to no electrocardiographic changes.

I hope that I may be forgiven for suggesting, on the basis of unpublished and unfinished experiments, that giving the proper degree of respiration to the curarised patient has received far too scant attention.

Selly Oak Hospital,
Birmingham.

JOHN CLUTTON-BROCK.

SIR,—I was much interested in the letter by Dr. Fajardo (Feb. 2) and the others which have followed.

I do not agree with Dr. Tobin's observation (Feb. 16) that hiccup arises from rough handling of the viscera by the surgeon.

In a personal series of 80 consecutive gastric operations which mostly included gastrectomy or vagotomy combined with some other procedure, usually antrectomy, and about 20 of which were for vagotomy alone, I have seen hiccup on only 3 occasions. Further, in the 20 vagotomies where traction on the œsophagus was considerable there was only 1 case of hiccup. Most of these resections have been subtotal.

I agree with Dr. Fajardo that hiccup is not necessarily associated with too light anæsthesia. But I cannot agree when he says that thiopentone and cyclopropane act, to some extent, as a causative agent, being vagotonic. Dr. Hendrie (March 1) points out that he has abolished hiccup by adding cyclopropane or thiopentone. In my series thiopentone, curare, cyclopropane, and oxygen, with as much of curare and as little of cyclopropane as possible, has been used. Curare was given to just "short of respiratory paralysis," as suggested by T. C. Gray and others in this country. With this sequence, in a personal series of over 1000 consecutive abdominal operations of various types during the last twelve months, with minimal assisted respiration (not controlled respiration), only the 3 cases of hiccup already mentioned were noted. Thus I do not agree with Dr. Hendrie that hiccup is commoner with assisted respiration.

As regards remedies, personally I have used 2–3 ml. of thiopentone or some more curare to the stage of respiratory arrest, and assisted the breathing for a few minutes until rhythmic respiration has started.

Manchester. RASHBEHARI GHOSE.

HERNIATION OF THE NUCLEUS PULPOSUS

SIR,—Mr. Charnley's article and the subsequent letters prompt me to mention some facts which may be unknown to many of those interested in the causes of disc prolapse.

An analogous condition occurs in dogs; but it differs from the human condition in certain respects, and the differences may be significant. Thus *in the dog there is a breed incidence*: it is common, for example, in the dachshund and the pekinese, in which the conjunction of a long spine with short legs places exceptional stresses and strains on the vertebral joints. In the dog prolapse of the disc is followed by calcification of the remaining structures, and so far the lesion has been confined to the thoracolumbar spine. I believe I am correct in saying that in man calcification occurs only in cervical prolapse.

Multiple prolapses are common in the dog, and each attack brings a recurrence of the original symptoms—pain and paraplegia or both. Paraplegia is very common, and complete posterior paralysis is not unusual. In a dachshund an X-ray film showed calcified discs in all the lumbar joints except one, and also in the lower thoracic joints. This animal had bouts of complete posterior paralysis with full recovery each time.

Some of these differences between the human and canine lesion may be attributed to the normal position of the spine—i.e., horizontal as compared with vertical. Occasionally spondylosis osteo-arthritica accompanies the lesion in the dog, and well-marked lipping is obvious on the ventral aspect of the vertebral bodies. So far as I am aware, surgical treatment in the dog has not been attempted in this country, but Olsen [1] describes cases relieved in this way. The operation is similar to that used in man, and it seems doubtful whether dogs do any better after operation than after other methods of treatment.

I used to believe that faulty skeletal conformation was an essential predisposing factor in the dog and that the condition developed when small repeated stresses acted on a fundamentally unsound structure typified in the dachshund. But the recent finding of a high incidence in cocker spaniels has made me consider more seriously the cause often held responsible in man—namely, a single violent overextension. In the dog, however, especially the cocker, this is much more likely to be a lateral movement than an anteroposterior (dorsoventr one; the violent wriggling movements with which t breed will greet a friend or show its pleasure are famili Perhaps different types of trauma must be accepted causes in different breeds. But I welcome Mr. Charnle hypothesis as offering an alternative explanation whi might apply to any of them.

Blackburn, Lancs. A. H. HOGG.

B.M.R. AND RADIO-IODINE TESTS IN DIAGNOS OF THYROID DISEASE

SIR,—Dr. Douglas Robertson (March 8) has question the value of radio-iodine tests in the diagnosis of thyr disease; and, in particular, he has extracted from paper [1] some data which, in his view, indicate gr discrepancies between our work in England and th of Keating et al.[2] at the Mayo Clinic. He, furth more, takes the opportunity to press again the val of the basal metabolic rate (B.M.R.) as a diagnostic t in clinical medicine.

The object of our paper was to compare and contrast relative value of several different techniques for the appli tion of radioactive iodine to the diagnosis of thyroid disea with especial emphasis on the diagnosis of thyrotoxico We compared tests measuring the total avidity of the gla for iodine (the peak and 24-hour uptake, and the 24-h urinary excretion of the isotope) with tests measuring the r of uptake (especially the thyroid-iodide clearance-rate devis by Myant et al.[3]) and with a test which measures the outp of hormone from the gland (the measurement of the prote bound plasma radioactivity 48 hours after a tracer dose).

We concluded that tests measuring gland uptake a clearance-rate separated normal persons (e.g., those wi no suspected thyroid abnormality, either anatomical functional) from those with thyrotoxicosis, but were of l value in differentiating many cases of mild hyperthyroidis from cases where thryotoxicosis was initially suspected b was eventually excluded after prolonged observation a study, including the effects of therapy. We found that t 48-hour protein-bound plasma activity value gave a positi index that correlated more closely than did the other te with the eventual clinical diagnosis. The test is, in essenc an index of the thyroxine content of the blood, which c only with difficulty be measured by chemical means.

As you, Sir, point out in your leading article, w included incidentally the results of the B.M.R. estimatio as carried out by us in the same series of cases. W were not primarily interested in the correlation of th B.M.R. with the clinical state of the patient; and, indee we did not include our results in the summary of ou paper. Dr. Robertson has queried the selection of "normal" range that extends from −20% to +20% This range is not based, as is the Mayo Clinic range −13% to +13%, on a statistical analysis of a larg series of cases; but it is a range which, from prolong clinical use, we have adopted because so frequent readings have been encountered at the extremes of th range in indubitably euthyroid individuals. On th basis, 33% of our thyrotoxic patients had B.M.R.s belo 20%, and 11% of our euthryoid patients had readin in excess of this. It is of interest that Professor Maclaga and his associates (March 8), who have made a detaile comparison of the B.M.R. with a useful radio-iodi test, have accepted a similar range of normality in department where they "have taken great care obtain reliable estimates and have required agreemen between duplicate determinations on the second da of test to within 5%." Nevertheless these worker like ourselves, show an appreciable number (14 out of th 52 cases in their figure, or 27%) of their thyrotox patients with B.M.R.s within the normal range, and out of 67 (12%) of their euthyroid or doubtful group with B.M.R.s in excess of +20%—figures that agree closely with ours.

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[1] Olsen, S. E. See *Vet. Rec.* 1951, 63, 740.

[1] Goodwin, J. F., Macgregor, A. G., Miller, H., Wayne, E. J *Quart. J. Med.* 1951, 20, 353.

[2] Keating, F. R., Haines, S. F., Power, M. H., Williams, M. M. *J. clin. Endocrinol.* 1950, 10, 1425.

[3] Myant, N. B., Pochin, E. E., Goldie, E. H. G. *Clin. Sci.* 194 8, 109.

Dr. Robertson has drawn attention to the observation of Keating et al. that 51% of their euthyroid group had a B.M.R. outside their normal range. We are fully aware of the selection carried out in the composition of their euthyroid group. In their own words: "The proportion of cases with basal metabolic rates outside the normal range is therefore a measure of the extent to which this group represents conditions in which the differential diagnosis of thyroid disease is not helped by determination of basal metabolic rate." It is in fact just that group for which a more precise, specific, and objective test is most desirable.

The other points regarding the B.M.R. which Dr. Robertson has raised have been covered in your leading article. It is of little help to the clinician to be forced to use a therapeutic test with iodine to assess the meaning of a particular B.M.R. estimation. The clinical response to therapy will be as valuable as the response of the B.M.R. and the purpose of the B.M.R. and of radio-iodine tests is to save the clinician the time, difficulties, and labour involved in the performance of a therapeutic trial.

In the table in his letter Dr. Robertson purports to show that, with respect to 24-hour gland uptakes of radio-iodine, we claim an absolute specificity for this test in the diagnosis of hyperthyroidism both in Graves's disease and toxic adenoma. To attribute to us such a claim, for which our data provide no shadow of evidence, is to convey an impression precisely the converse of that given in our paper. Moreover, it implies a misconception of the probable scope and validity of any diagnostic test of thyroid function. Throughout his whole letter Dr. Robertson completely ignores the existence of the "intermediate" group studied in our paper. This group consisted of those patients in whom suspicions of hyperthyroidism had been aroused by one or more features, but which eventually proved to be euthyroid clinically. When this group is considered, our paper shows clearly that 24-hour gland uptakes are most unsatisfactory as a diagnostic measure; and we state that "the degree of overlap is such that we feel the test is of less value in the difficult intermediate group of cases." Dr. Robertson has taken the unusual course of quoting as our evidence of the value of radio-iodine tests a particular application of the technique which we were at pains to show to be among the least satisfactory.

Furthermore, he claims to show that we differ from Keating et al. in our opinion of the value of radio-iodine tests in the diagnosis of toxicity in adenomatous goitres. Dr. Robertson has ignored our statement that

"in the case of toxicity due to the presence of an adenoma, the amount absorbed by the gland is of less diagnostic value than when the thyrotoxicosis is due to diffuse enlargement of the gland. This conclusion agrees with that of Keating et al. (1950) that . . . tracer tests for radioactive iodine, as carried out by them, were of limited value in indicating the presence or absence of hyperthyroidism in cases of adenomatous goitre."

Dr. Robertson does not mention that the measurement of the concentration of radioactive protein-bound iodine in the blood after a tracer dose may prove to have more diagnostic value than the measurement of iodine accumulation in the gland. Such a test was described in our paper and reference made to other work in this field. The method has the great advantage that it can be carried out as a diagnostic measure without admission of the patient to hospital. It involves minimal inconvenience to the patient, who is subjected to no more than a venepuncture. In our opinion it has a diagnostic value in the untreated patient in excess of that of the B.M.R.

The problem for the future is to decide which of the many tests of thyroid function is of the greatest assistance to the clinician, and which can be safely, conveniently, and easily performed. We feel confident that the most hopeful line of approach is the study of the secretions of the thyroid gland rather than investigations which yield indirect evidence only.

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A. G. MACGREGOR
E. J. WAYNE.

Sheffield National Centre for Radiotherapy.
H. MILLER.

Postgraduate Medical School,
Hammersmith Hospital, London.
J. F. GOODWIN.

ANÆMIA IN AFRICANS

SIR,—In my earlier letter (Jan. 12) I stated that Dr. Foy and Dr. Kondi had said that reticulocytes were larger in Africans than in Europeans. This was a misapprehension on my part, and is incorrect. There would appear to be no information about the size of reticulocytes in the African compared with the European.

Mulago Hospital,
Kampala, Uganda.
P. W. HUTTON.

FACTS AND FIGURES ON ALCOHOLISM

SIR,—One point in Dr. Pullar-Strecker's interesting article last week deserves comment. Comparison of alcoholism-rates with the annual alcohol consumption in different countries cannot be interpreted as indicating difference in the "head" for alcohol of the different populations without due regard to their methods of drinking and types of drink taken. In the Scandinavian countries it is customary to take mainly spirits, on an empty stomach; whereas in Italy the main alcohol consumption is in the form of wine, largely taken with meals. This difference would of itself tend to produce the results quoted.

Careful comparison of a large sample of various nationalities under laboratory conditions would be necessary before one could be certain that a real difference existed in their capacity to take alcohol without deleterious effects.

Department of Physiology,
University College, London.
M. GRACE EGGLETON.

ANÆSTHESIA FOR TUBERCULOUS PATIENTS

SIR,—What anæsthetic should be chosen for a patient who happens to have pulmonary tuberculosis is still a vexed question. That the present approach to this problem may not be altogether rational was once again brought home to me recently on hearing about a young, vigorous, and healthy-looking girl of 20, who had recently been discharged from a sanatorium.

She was to have a straightforward appendicectomy for acute appendicitis. The patient's history, in conjunction with common present-day teaching on these matters, led the anæsthetist, an earnest but comparatively inexperienced registrar, to choose spinal anæsthesia. The girl became somewhat hysterical soon after the injection had been made, and only after over 1·0 g. of thiopentone had been administered intravenously could the operation begin. Not surprisingly perhaps, the patient collapsed, and eventually cardiac massage was carried out. Happily, after two days of anxiety the patient recovered and is apparently well today. She was literally snatched from death.

Yet all over the country various pulmonary operations of great complexity and of long duration are performed for tuberculosis under inhalation anæsthesia. While the mechanical and physiological measures to combat the problems posed by the pneumothorax, the control of secretions, and the spread of the disease, occupy the attention of anæsthetists, little discussion ranges round the choice of drugs in these cases, although nearly every anæsthetic and method has its advocate somewhere. Even the much-maligned ether (although it is not my own practice) is the anæsthetic of choice in a few centres, some of international repute.

In view of such cases as that described above and the widespread use of inhalation anæsthesia for the surgery of pulmonary tuberculosis, it seems a little unwise to emphasise in the training of anæsthetists and surgeons that inhalation anæsthesia must not be used in these patients for operations on other parts of the body. It is questionable whether by avoiding an inhalation anæsthetic spread of the disease is prevented; for even with regional anæsthesia the patient must inhale—in this case, air.

It would be helpful if anæsthetists and general surgeons, with experience of anæsthetising and operating on patients with pulmonary tuberculosis, would record any evidence of the influence of inhalation anæsthesia on the disease.

Department of Anæsthetics,
Welsh National School of Medicine,
Cardiff.
WILLIAM W. MUSHIN.

ATROPINE IN CANCER

SIR,—I am collecting information about the action of atropine and its derivatives in the palliative treatment of cancer; but the literature does not seem to contain any references in this respect, and I should be grateful for any information. The theoretical rationale for using atropine is the abnormal phospholipid (choline) metabolism of tumour tissue with the possible production of abnormal choline metabolites, the action of which may contribute to the nervous manifestations of cancer cachexia, and may be inhibited by the choline antagonist, atropine.

Franklin Park, New Jersey, U.S.A. AUGUST HOLM.

ARTIFICIAL RESPIRATION

SIR,—In your concise leading article last week you suggest that Schafer's method be officially replaced by a modification such as Nielsen's. I, for one, would strongly object to this.

The greatest use, today, of Schafer's method is in the treatment by first-aiders of the acute asphyxias, where the most urgent need is to fill the lungs with respirable air. Thousands of first-aiders have been trained to do this efficiently; some, I know, in emergency have borrowed Nielsen's technique at the same time, in order to increase chest movement where muscle relaxation has gone too far. They have been taught that the sooner the lungs can be made to inspire enough air to make the respiratory centre respond to the stimulus of carbon dioxide, the sooner will the patient be fit for removal to hospital. The first-aider does not need to know the tidal volume, and so forth. These details vary according to the patient—as those of us know who saw the "lab. boy" of Schafer's department in Edinburgh, nearly bursting the spirometer out of loyalty to his chief.

The principles of Schafer's method are well known in this country; they can be carried out, single-handed, as quickly as any other method, and are efficient. Speed is the great factor in success, and in my opinion it would be wrong to introduce another school of thought to those thousands who can carry out the Schafer technique efficiently.

Hemel Hempstead, Hertfordshire. GILBERT BURNET.

SIR,—Inspired by work in the University of Illinois, I have for the past sixteen months been teaching the Nielsen (arm-lift/scapular-pressure) method to boys of various ages, in several scout troops. I find that they readily appreciate the advantages of the method and that it is easily taught. Small boys are able to obtain better ventilation than with Schafer's method. Such methods as hip-lift and Silvester's are beyond the strength of most of the smaller boys.

A wider dissemination of knowledge concerning the Nielsen method is overdue, and your leading article will, I hope, bring it to the notice of doctors teaching first-aid.

London, S.W.1. R. E. C. COPITHORNE.

OUR ATTACK OF INFLUENZA

SIR,—The following is an account of unusual at of "influenza."

On Jan. 24 my wife visited a friend and found her in bed on the first day of a "cold." 5 days later my wife's ton teeth became more tender. Another 5 days later she felt giddy, so stayed in bed for several hours. Infection of semicircular canals? Teeth tenderness disappeared and has not returned. On the same and the following day I felt poorly.

During the next week my wife was sleepy, even at breakfast; and on the 15th day she had a temperature of 100°F and remained in bed all day—drowsy, but with no pain or cough. Since then she has been normally active despite some altogether new neuritis in her thigh.

My malaise continued, and my chronic bronchitic cough and sputum increased somewhat in the cold weather. Suddenly, on Feb. 18 (20th day from Jan. 29) at 10.30 A.M., after finishing a light surgery, I experienced definite shivers. My temperature was 100·4°F and I went to bed. I took gr. 10 aspirin, which did not make me perspire. At 5 P.M. I had a temperature of 101°F, with pain in my side and several twinges to the left acromion; and I wondered if I should not have taken some sulphonamides. At 9 P.M., however, I started sweating for two hours, and next morning the temperature was normal. I am glad I did not take sulphonamides as I would have wrongly attributed the early crisis to them. On Feb. 26 I had enteritis—a relapse—but no pyrexia or increase of sputum.

It appears that the incubation period of this infection is 5 days, and that it comes on in increased waves—like the larger formations of sporozoites in untreated malaria—culminating in a pyrexial attack. After an interval of about a week it is followed by one or more relapses of varying sorts. In some subjects it attacks the nervous system centrally and/or peripherally.

Epsom, Surrey. M. J. ROCHE.

GAS-AIR ANALGESIA MACHINES AND THE "C.M." ATTACHMENT

SIR,—In the recent excellent publication *The Relief of Pain in Childbirth*, Professor W. C. W. Nixon and Miss Shila Ransom state with reference to nitrous-oxide/air analgesia machines for self-administration:

> "The Chassar Moir attachment is an attempt to provide pure gas at the beginning of a pain, in itself an excellent idea. It is of $2^1/_2$ litre capacity and is filled by an extra flow of gas at the rate of 1 litre a minute."

I should like to make it clear that there is no such device bearing my name.

In 1938, at the suggestion of Dr. John Elam,[1] the Dental Manufacturing Company produced a machine giving a pure-gas/gas-air sequence. Later the British Oxygen Company introduced a Minnitt machine with what they called a "C.M. attachment." What the initials stood for I was *never told*. I was *not* approached by the company in this matter, although later, for private purposes, I tested these apparatus both in its standard form and also in a modified version produced at my request.

As it seems that my name, rightly or wrongly, is not connected with the use of the special attachment I should like to make a few comments on the subject.

The idea of the reservoir bag was based on a clinical investigation made in 1936.[2] I proposed that safety in self-administration might be obtained by limiting the *quantity* of gas as an alternative to limiting the *concentration* of gas—the method previously used. I found that a bag of approximately 3 litres capacity (2–3 deep breaths) was suitable; and that this amount of gas (and nothing further) inhaled at the onset of each uterine contraction caused an analgesia which was decidedly more prompt and effective than that obtained with the customary gas-air mixture. A machine embodying this principle was put into use; and over the years since then I have been convinced of its superior action.

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1. Elam, J. *J. Obstet. Gynæc.* 1939, 46, 61.
2. Moir, C. *Lancet*, 1937, i, 615.

Regarding the sequence of pure gas and gas-air, I have also made experiments (unpublished) with small reservoir bags of pure nitrous oxide followed by permissible concentrations (up to 50%) of gas and air. The results were superior to those obtained with the usual gas-air apparatus but not, it seemed to me, substantially better than those obtained with my earlier pure-gas method, which had, of course, the advantage of simplicity. This, too, has been the experience of Stig Karlsen, of Stockholm, who has also investigated the subject.

The capacity of the bag added to the Minnitt machine by the British Oxygen Company is approximately 2 litres—less than is stated by Nixon and Ransom. If this size is much exceeded the large quantity of pure gas plus the later prolonged inhalation of a 50% gas-air mixture may cause severe anoxæmia.

In recent years the position has changed. The new Warming machine (mentioned but not named in Nixon and Ransom's book) automatically supplies a fixed and optimum percentage of nitrous oxide and oxygen; the useless atmospheric nitrogen is excluded, and the permissible amount of nitrous oxide can therefore be much increased. This machine has, in my opinion, superseded gas-air and pure-gas apparatus for hospital use. As Seward[3] has shown, satisfactory analgesia is easily maintained, and maternal anoxæmia—so dangerous to the fœtus—is entirely eliminated. It is in this direction that the future of gas analgesia seems to lie—not in the use of "attachments," which some may suppose were sponsored by myself.

Nuffield Department of
Obstetrics and Gynæcology,
Radcliffe Infirmary, Oxford.

J. CHASSAR MOIR.

Obituary

CHARLES KILLICK MILLARD

M.D., D.Sc. Edin.

Dr. Killick Millard, for 34 years medical officer of health for Leicester, was all his life interested in the practice and principles of public health, but he was perhaps best known for his views on vaccination. A year ago in our columns he suggested that the discrepancy between his position and orthodoxy lay in the distinction he drew between "the effect of vaccination upon the individual and its effect upon the community." Recent vaccination, he held, protects the individual, yet by masking the disease vaccination might actually promote the spread of smallpox in the community.

Dr. Millard was born in 1870, one of the nine children of the Rev. C. S. Millard, rector of Costock, Notts. He was educated at Trent College and the University of Edinburgh, where he qualified in 1892. After a year's postgraduate work in London he took his B.SC. in public health in 1893. The following year he was appointed resident medical officer at the Birmingham Fever and Smallpox Hospitals at a time when a serious epidemic of smallpox was at its height. This clinical experience of the disease led him to choose it as the subject of his M.D. thesis in 1896. The same year he was promoted superintendent of the Birmingham Fever Hospital, a post he held till in 1899 he became medical officer of health for Burton-on-Trent.

When he applied for the post of M.O.H. at Leicester in 1901 his experience of smallpox, he believed, helped him to obtain the post. Some fifteen years earlier the town had abandoned compulsory vaccination, and Dr. Millard himself later described it as the Mecca of the anti-vaccination movement. At the time of his appointment he could still describe his views on vaccination as orthodox, but his experience in the smallpox outbreaks of 1902–03 confirmed his doubts as to the necessity for universal vaccination.

Dr. Millard did not allow his interests in public health to become limited to this one absorbing topic. His annual reports were always lively reading, and his enthusiasm for better housing led him to act as informal counsellor and honorary gardening consultant to the new tenants of municipal schemes. He supported propaganda for birth control at a time when it was condemned by many, and he made it the subject of his presidential address to the Leicester Literary and Philosophical Society in 1917. He filled many presidential chairs in the town, and besides the Leicester Medical Society he was also president of the Leicester Rotary Club and the Leicester Temperance Society. In his later years he became interested in voluntary euthanasia, and in 1931 he chose this as the subject of his presidential address to the Society of Medical Officers of Health. In 1934 he founded the Voluntary Euthanasia Legislation Society, of which he remained secretary until his death.

Dr. Millard's relinquishment of his post as M.O.H. could hardly be called retirement. At 62, for instance, he took up flying and he obtained his pilot's certificate. He celebrated his 80th birthday by giving himself a motor-bicycle on which he rode the 1000-odd miles from Leicester to Inverness and back. Though he had been brought up in the Church of England, for the last 40 years of his life Dr. Millard was a member of the Unitarian Church, and for several years he had been chairman of the vestry of the Great Meeting Chapel at Leicester. His garden also claimed a rather larger share of his time, which meant he was able to give even more vegetables, fruits, flowers, and honey to his friends and colleagues. During the late war he gave up all pretence of retirement and became temporary M.O.H. for the Blaby and Lutterworth districts, a post he held until last year.

Dr. Millard is survived by two daughters and two sons, one of whom is in general practice in Leicester.

WILLIAM MARTIN MUIRHEAD

M.B. Sheff., D.O.M.S.

Mr. W. M. Muirhead, who had held office in the North of England and the Midland ophthalmological societies, died at his home in Sheffield on March 4 at the age of 64.

He was educated at Wesley College, Sheffield, and Sheffield University, where he graduated M.B. in 1911. After holding resident posts at the Sheffield Royal Hospital he became interested in ophthalmology and held a post in that specialty which would now be called a registrarship. In 1916 he joined the R.A.M.C., in which he served till 1921, for much of the time as an eye specialist. After he was demobilised he worked for two years in the anatomy and physiology departments at Guy's and St. Thomas's Hospitals and he passed the primary fellowship examination. Later he went through the traditional outpatient and resident posts at Moorfields, and he took the D.O.M.S. in 1927.

In that year he was appointed ophthalmic surgeon to Chesterfield and North Derbyshire Royal Hospital, and this appointment, along with that of oculist to Chesterfield education committee, he held until his death. By 1939 he had also joined the staffs of the Rotherham and Worksop Hospitals, and he was joined in practice by his brother.

G. M. writes: "*A man of excellent clinical sense and unwearying work, Muirhead maintained his interest in scientific ophthalmology and cherished his links with the London of his training years and the chiefs he had served there. As secretary of the North of England Ophthalmological Society from 1935 onwards he was an outstanding success, and he maintained the activity and traditional influence of this society. To these duties he last year added the treasurership of the Midland Ophthalmological Society. Meetings of ophthalmological societies—their scientific interest and the personal associations they offered—were a delight to him and it was unusual for him to miss any meeting in London and unthinkable if it was in the Midlands or North. To travel with him in the United Kingdom or abroad was a constant pleasure, and incidentally a guarantee that all doors would be opened in welcome. The kindliness of his nature shone in all he did, but it was only in working with him on a committee that one came to realise his thoughtfulness and his skill in planning to draw out and encourage the diffident or neglected, or neglectful, member. His modest, kindly, and widespread influence was a unifying factor amongst British ophthalmologists, and while many will miss him on personal grounds, many more will feel his loss to the specialty.*"

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3. Seward, E. H. *Proc. R. Soc. Med.* 1949, 42, 745.

MICHAEL HESELTINE

C.B.

FROM the time when he joined the National Health Insurance Commission in 1912 and became private secretary to Sir Robert Morant, Mr. Heseltine had a great deal to do with doctors; and as registrar of the General Medical Council from 1933 till last year he was a loyal friend to the profession. Born in 1886, the son of a parson, he was educated at Winchester and New College and entered the Civil Service in 1909. Before going to the Ministry of Health in 1919, he gained diverse experience in the Office of Works, the Home Office, the Ministry of Munitions, and the Ministry of Reconstruction, and he was appointed C.B. in 1919 at an age when such honours are rarely attained. His ability was used by making him secretary of a considerable number of special inquiries, some of them of first-rate importance, including Lord Addison's committee on the proposal for a Ministry of Health, Lord Haldane's committee on the machinery of government, Lord Dawson's council on medical and allied services, the Royal Commission on Local Government of Greater London (Lord Ullswater), and the Royal Commission on Local Government (Lord Onslow). In 1928, when an assistant secretary in the Ministry of Health, he became a member of the Dental Board, and before he entered the whole-time service of the board and the G.M.C. he had been secretary of the Postgraduate Medical Education Committee, of the committee charged with establishing the British Postgraduate Medical School, and of the medical advisory committee dealing with alleged negligence by National Health Insurance doctors. Thus he went to the council knowing much both of medical education and medical discipline, and it was not long before he became its learned, devoted, and always distinguished servant. He will be remembered both for his sound work and for himself; for he was a man curiously and charmingly mixed, in whom a frail appearance, a deprecating voice, and a great respect for precedent and the letter of the law were associated with a strongly characteristic handwriting, high intelligence, much kindness, and a gay wit.

Births, Marriages, and Deaths

BIRTHS

Arden.—On March 9, at Alverstoke, the wife of Surgeon Commander L. D. Arden, R.N.—a daughter.

*Black.—On Feb. 18, in Birmingham, Dr. Margaret Black (née Fallon), the wife of Dr. Alan Black—a son.

Brady.—On March 8, at Colchester, the wife of Dr. Thomas Brady—a daughter.

Dingley.—On March 6, at Bromley, Kent, the wife of Mr. A. G. Dingley, F.R.C.S.—a son.

Eve.—On March 10, at Seascale, Cumberland, the wife of Dr. I. S. Eve—a son.

Fagg.—On March 10, at Hitchin, the wife of Dr. C. G. Fagg—a daughter.

Habibis.—On March 2, in London, Dr. Stella M. Habibis (née Murray), the wife of Dr. H. S. Habibis—a daughter.

Paton.—On March 11, the wife of Dr. Alex Paton, of Sutton, Surrey—a daughter.

Scott.—On March 7, in London, the wife of Dr. Oliver Scott—a daughter.

MARRIAGES

Carré—Forshaw.—On Feb. 23, at Weybridge, Surrey, Ivo John Carré, M.B., M.R.C.P., D.C.H., to Pamela June Sutherland Forshaw.

Paterson—Knight.—On Jan. 23, in Hong-Kong, Edward Hamilton Paterson, M.B., F.R.C.S., of Eltham, to Barbara Knight, B.SC., of Tewkesbury.

DEATHS

Blakely.—On Feb. 24, at Sheffield, John Blakely, M.B. Glasg.

Doorly.—On March 13, Arthur Rawdon Carrington Doorly, M.B. Lond., of Surbiton.

Fedden.—On March 12, in London, Walter Fedde Fedden, M.S. Lond., F.R.C.S.

Findlay.—On March 14, George Marshall Findlay, C.B.E., D.SC. M.D. Edin., F.R.C.P., of Radlett, Herts, aged 59.

Munden.—On March 8, at Stroud, Glos, Marwood Mintern Munden, M.R.C.S.

Osburn.—On March 7, at Bournemouth, Arthur Carr Osburn, D.S.O., B.LITT. Oxfd, M.R.C.S., lieut.-colonel, R.A.M.C. retd, aged 75.

Stockwell.—On March 9, in Leeds, George Ephraim St. Clair Stockwell, T.D., M.B. Camb., aged 75.

Whyte.—On Feb. 27, at Leicester, Alexander Whyte, M.B. Glasg., D.P.H.

* Amended notice.

Appointments

Macleod, J. G., M.B. Edin., F.R.C.P.E. : part-time physician, Roy Edinburgh Hospital for Mental and Nervous Disorders.

Young, R. V., B.M. Oxfd : asst. pathologist (S.H.M.O.), Banb H.M.C. area.

Birmingham Regional Hospital Board :

Bedford, G. T., M.B. Edin., D.O.M.S. : whole-time consulta ophthalmologist, Birmingham (Selly Oak) and Birmingha (Mental D) groups.

Dolton, E. G., M.B. Lond., F.R.C.S. : part-time consul thoracic surgeon, Wolverhampton group.

Finkelstein, Z., M.D. Warsaw, D.P.M. : asst. psychiatri Highcroft Hall Hospital.

Macdonald, A. W. B., M.B. Aberd., B.SC. : whole-time consulta chest physician, Dudley and Stourbridge group and Dud county borough council.

MacHale, S. J., M.B. N.U.I., B.A.O., F.R.C.S. : part-time consulta thoracic surgeon, Birmingham (Sanatoria) and Mid-Worcest shire groups.

Paine, D. H. D., M.B. Lond., D.P.M. : consultant psychiatri and medical superintendent, St. Margaret's Hospital, Gr Barr.

[illegible] M.B. Lond., D.A. : part-time consulta [illegible] Plastic Surgery Unit, Words

[illegible] And., F.R.C.S. : part-time consulta E.N.T. surgeon, Stafford and Mid-Staffs (Mental) groups.

Russell, A. W., M.D. Glasg., D.P.H. : whole-time consulta chest physician, West Bromwich group and Smethwi county borough council.

Colonial Service :

Cameron, D. M., M.B. Edin. : M.O., North Borneo.

Carson, A. A. G., M.B. Belf. : M.O., Tanganyika.

Fowler, A. F., M.R.C.S., D.T.M. & H. : senior M.O., Uganda.

Gillespie, T. H. F., M.B. Dubl., F.R.C.S.I. : special grade M.O Kenya.

Heycock, M. H., M.B. N.Z., F.R.C.S.E. : M.O., Federation of Malay

Macdonald, Neil, M.B. Lond. : M.O., Federation of Malaya.

Regester, P. T., M.R.C.S. : M.O., North Borneo.

Relvich, A. L., M.D. Kraków, D.T.M. & H. : M.O., Leprosy Servic Nigeria.

Renner, E. A., O.B.E., M.D. Edin. : D.M.S., Sierra Leone.

Taliadoros, D. M., M.D. Athens : M.O. specialist (gynæcologi Cyprus.

Thomson, W. G., M.B. : M.O., Federation of Malaya.

Tizard, D. A. T., B.M. Oxfd : M.O., Uganda.

Toomey, D. J., M.B. Madras, F.R.F.P.S., F.R.C.S. : M.O. (Grade A Gibraltar.

Wills, F. E. B., M.B. : M.O., Medical Department, British Guian

Leeds Regional Hospital Board :

[illegible] Edin., D.M.R.T. : consultan [illegible] service.

[illegible] asst. geriatric physicia [illegible]

Raper, F. P., M.B. Leeds, F.R.C.S. : consultant in neurologica surgery, General Infirmary, Leeds, and St. James's Hospita Leeds.

Watt, Alexander, M.B. Aberd. : asst. psychiatrist (S.H.M.O.) *Broadgate Hospital, Beverley.*

Newcastle Regional Hospital Board :

Coleman, P. N., M.B. Birm. : consultant pathologist, Nort Allerton H.M.C. group.

Lower, E. S., M.R.C.S. : asst. psychiatrist, Aycliffe Menta [illegible] al group.

[illegible] M.B. Edin., D.M.R.D. : consultant radiologi [illegible] H.M.C. group.

[illegible] Lond., D.P.H. : consultant chest physicia Durham area.

Robertson, J. M., M.B. St. And. : consultant pathologist, South West Durham H.M.C. group.

Tweedy, T. H., M.B. Durh., F.R.C.S. : consultant surgeon Gateshead H.M.C. group.

North-East Metropolitan Regional Hospital Board :

Barclay, G. A., M.A., M.B. Camb., F.R.C.S. : part-time consultant surgeon, St. Andrew's Hospital, Bow.

Gilbert, Irving, M.D. Lond., M.R.C.P. : part-time consultant physician, St. Andrew's Hospital, Billericay.

Hal[illegible] D.C.H., D.A. : part-time [illegible] th Hospital for Children.

Jon[illegible] : full-time consulta surgeon, Colchester group of hospitals.

Linsell, W. D., M.D. Lond. : full time consultant-pathologist, group laboratory, Mile End Hospital.

Mason, A. S., M.A., M.B. Camb., M.R.C.P. : part-time consultan [illegible] Hospital.

[illegible] .S. : maximum part-time [illegible] ssex Hospital and annexe.

[illegible] Lond., F.R.C.S. : part-time con [illegible] Wales's and St. Ann's Hospitals.

[illegible] : part-time consultant E.N.T. [illegible] and Runwell Mental Hospitals.

Sheffield Regional Hospital Board :

Kinmouth, M. H., M.B. Lond., F.R.C.S. : consultant plastic surgeon to the board.

Sherburn, V. E., M.B. Manc. : medical director, South Yorkshire [illegible] unit.

[illegible] M.B. Leeds, D.M.R.D. : consultant radiologist. [illegible] ral Hospital.

The Terms and Conditions of Service of Hospital Medical and Dental Staff apply to all N.H.S. hospital posts we advertise, unless otherwise stated. Canvassing disqualifies, but candidates may normally visit the hospital by appointment.

Notes and News

THE CIBA FOUNDATION

WHEN the headquarters of the foundation at 41, Portland ce, London, W.1, were opened in June, 1949, Lord veridge, one of the trustees, described it as "a place where people who are working on research can meet together discuss their problems . . . in pleasant and comfortable rroundings." The report of the foundation for 1951 tells w the work of promoting international coöperation in edical and chemical research is continuing. During the year sitors from 26 countries have been present at conferences, eetings, or lectures at Portland Place, or have been the ests of the foundation while attending to scientific work London. Some of the visitors led informal discussions on bjects of their own choosing among guests interested similar research. The subjects for the formal conferences the year included Hormonal Influences on Water Metaolism, Isotopes in Biochemistry, and Visceral Circulation. he proceedings of 12 of the conferences held since the undation opened have been or are being published by essrs. J. & A. Churchill in London and by the Blakiston ompany of Philadelphia in the United States.

CHELSEA CLINICAL SOCIETY

EACH of London's many medical societies has its own articular characteristics and atmosphere. None has developed happier individuality than the Chelsea Clinical Society. Even its name is something apart from the ordinary run; or half its members are addressed not in S.W.3 but in W.1, nd anyhow it meets not in Chelsea but South Kensington; nd furthermore its meetings are rarely clinical. Now in ts 55th year, this society combines successfully convivial atherings at the dinner table with not too energetic discussion of medical, paramedical, and even frankly nonedical topics; and lately the subjects have ranged from he goings-on at Scotland Yard to war-time adventures with he Maquis and a first-hand account of an Everest expedition these last two both by members).

On March 11 the speaker was Dr. R. E. Smith, erstwhile medical officer to Rugby School, who contrasted present-day conditions at public schools with those that prevailed half a century and more ago. Thanks largely to the late Dr. A. I. Simey and to Dr. G. E. Friend, schools now provide a substantial evening meal; and they are fortunate in obtaining the food for midday meals as an extra to the usual rations. Dr. Smith went on to suggest that the ordinary infectious diseases are largely inevitable, and that boys should have them as early as possible. One benefit from the improved nutrition is enhanced resistance to such infections. In a recent outbreak of measles, not one of 80 boys with the disease had catarrhal symptoms, and only 1 had otitis media. Similarly Sonne dysentery has become less serious, and there is less liability to fractures, boils, and heart-disease, and to disorders of the blood, kidney, and lung. Dr. Smith said that the school doctor must be firstly a physician, secondly a surgeon, and thirdly a psychologist. In one way he was more handicapped than the family doctor; for he did not know the parents as he should.

RESEARCH ON TWINS

THE monograph,[1] by Prof. Luigi Gedda, of Rome, on the study of twins, has been followed by the appearance of a new journal,[2] under his editorship, dealing with medical genetics and the study of twins. This journal is to be published three times a year, and authors may choose the language in which their articles are printed; but each article is to end with a summary in English, Italian, French, and German. The usefulness of twin studies for elucidating the nature-nurture problem, originally propounded by Galton, has sometimes been over-estimated, and comparison of monozygotic and dizygotic twins has often yielded trivial or ambiguous results. Nevertheless the difficulties of human genetics are so great at no path to knowledge should be neglected. Perhaps the concentration of twin studies in this lavish journal will inaugurate a new and more critical era in this field.

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[1] Gedda, L. Studio Dei Gemelli. Rome, 1951. See *Lancet*, 1951, ii, 296.

[2] *Acta Genetica Medica et Gemellologia*. Largo Amba Aradam 1, Rome. Subscription 5000 lire (£5) per annum, or 2500 lire for a single issue.

WEEKEND DISEASES

A SYMPOSIUM[1] by Dr. G. E. Beaumont's clerks gives a useful picture of the conditions for which casualty treatment over the weekend is sought at a large London hospital. Dental emergencies form a large part of the casualty attendances; for "*most patients consider the doctor is the one to see at* unusual hours, rather than the dentist." Rugby football is a potent source of casualties. Alcoholism may still produce the case of acute retention or the ruptured over-full bladder, and the need for careful examination to exclude other causes of coma is duly emphasised; Saturday-night paralysis has a section to itself (it would be interesting to know whether this is common enough to warrant the attention it receives in textbooks). Hay-fever and urticaria from exposure to pollen, insect-bites, or "ingestion of shellfish at Southsea" are good examples of weekend risks run by the town-dweller who ventures into the country. Bronchial or cardiac asthma may come on after a late and heavy supper on Sunday.

University of Cambridge

On March 8 the following degrees were conferred:

M.D.—C. F. Barwell, S. C. Gold, * J. P. Henry, A. S. Mason, * J. G. Selwyn.

M.B., B. Chir.—* J. H. F. Batstone, T. H. Morgan.

* By proxy.

University of London

Dr. W. D. M. Paton has been appointed to the readership in pharmacology and therapeutics at University College and University College Hospital Medical School.

University of Glasgow

On Wednesday, April 16, at 4.30 P.M., Dr. William Pickles will deliver the Noah Morris lecture. He is to speak on Epidemiology in Country Practice.

University of Dublin

Prof. S. P. Bedson, F.R.S., has been appointed John Mallet Purser lecturer for 1952. It is hoped that he will deliver the lecture in May.

Royal College of Surgeons of England

At a meeting of the council held on March 13, with Sir Cecil Wakeley, the president, in the chair, Mr. C. W. Flemming was admitted to the court of examiners. A Hunterian professorship was awarded to Mr. K. W. Starr. The Hallett prize was presented to Dr. J. C. N. Wakeley, and the award of a Streatfield research scholarship to Mr. A. T. Andreasen *was reported.*

A diploma of fellowship was granted to A. O. Parker, and a diploma of membership to A. P. Coats Bacon.

Royal Society of Medicine

Mr. R. T. Hewitt, O.B.E., M.A. Oxfd, has been appointed secretary of the society.

Royal Society of Edinburgh

A David Anderson-Berry medal, with a prize of about £100, will be awarded in 1953 by the society for work on the therapeutic effect of X rays on human diseases. Published and unpublished work may be submitted and should reach the general secretary of the society, 22, George Street, Edinburgh, 2, by March 31, 1953.

Mental After Care Association

The annual meeting will be held at the rooms of the Royal Society, Burlington House, Piccadilly, London, W.1, on Friday, March 28, when Sir Percy Barter, chairman of the Board of Control, and Dr. Henry Yellowlees, chairman of the association, will speak.

General Practice in the Curriculum

With the help of the local medical committee for Birmingham, the board of the faculty of medicine of the University of Birmingham has arranged an experimental scheme by which students may gain experience of general practice. It is proposed that at a convenient time during the last two years of their clinical course students shall spend two weeks as assistant to a general practitioner. During this fortnight they will be excused from hospital work and university lectures, but not from courses at which attendance is compulsory. The scheme is a voluntary one; but, as the students have often asked for it to be started, the board hopes for a good response.

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[1] *Middlesex Hosp. J.* 1952, 52, 7.

Congress of Oto-neuro-ophthalmology

This international congress will be held at Lisbon from April 22 to 26. Further particulars may be had from the secretary-general, Dr. Auguste Tournay, 58, rue Vaugirard, Paris, VI.

Queen's Commendation

Flying-Officer G. A. Faux, M.R.C.S., R.A.F., has received the Queen's commendation for brave conduct while caring for an injured man in a burning aircraft.

Care of Old People

The National Old People's Welfare Committee will hold a conference on this subject in Scarborough from April 3 to 5. The speakers will include Dr. T. S. Hall, Dr. Trevor Howell, and Dr. L. G. Norman. Further particulars may be had from the secretary of the committee, 26, Bedford Square, London, W.C.1.

Anglo-Danish Sanatorium Scheme for Children

Through the generosity of the Anglo-Danish Society, a first party of 25 British tuberculous children has left for treatment at Vordingborg Sanatorium, Denmark. The children have been selected by the medical committee of the National Association for the Prevention of Tuberculosis. The British Red Cross Society is coöperating in the arrangements for travel, escort, and welfare. Though the scheme is a private one it has the approval of the Ministry of Health. The ages of the children range from eight to fifteen. There are 14 boys and 11 girls. Most of them come from the London metropolitan area and a few from Birmingham and Oxford.

Minister on Economy in Prescribing

Mr. Harry Crookshank, the Minister of Health, speaking at the annual dinner of the Lincoln division of the British Medical Association on March 14, said that the most worrying of all the items of expenditure in the National Health Service was the drug bill. "It is surely out of all proportion that out of a total expenditure on the whole service in Great Britain . . . one-eighth, or over £50 million a year, should be spent on the drugs prescribed by general practitioners and dispensed by chemists." The most alarming feature of this expenditure was that it had increased steadily every year since the service started. The increase had been a double one—an increase both in the number of prescriptions and in the average cost of each prescription. Last year the number of prescriptions in England and Wales alone was just on 230 million, and the estimated average cost was over 3*s.* 8*d.* The drug bill had in fact got out of control, and it was for this reason that the Government proposed a shilling charge on prescriptions, as announced by the Chancellor of the Exchequer in January. "I appreciate that this will involve certain difficulties for certain doctors, especially in rural areas, but these I hope to discuss with the British Medical Association next week. The wider question raised by what has happened is whether all this prescribing is really necessary. Most doctors, when speaking generally, seem to say No, but it is much more difficult to apply this maxim to the individual case, where many factors come into play. There may be pressure by the patient, convinced that he cannot get better without a 'bottle,' or high-powered salesmanship by the travelling representatives of the drug manufacturers, or the difficulties today experienced by the doctor in ascertaining the cost of prescribing. . . . To patients I would say: 'Your doctor knows best what is good for you; do not press him for any particular medicine you may fancy; pay more attention to what he advises; surely in the present educated age we should have outgrown the "bottle" habit; and, anyhow, you really have no right to ask the doctor for remedies intended for self-medication, and the doctor is under no obligation to supply such remedies.' To doctors I would say: 'Your best protection against high-powered and sometimes over-enthusiastic salesmanship is knowledge of the cost of prescribing.' . . . We are producing a short bulletin, to be issued periodically, which is intended to convey to doctors in a brief and readable form outstanding facts about the cost of prescribing. The first number is now about to be distributed."

EMERGENCY BED SERVICE.—In the week ended last Monday applications for general acute cases numbered 989. The proportion admitted was 87·0%.

Diary of the Week

MARCH 23 TO 29

Monday, 24th

SOCIETY OF ENDOCRINOLOGY
5.30 P.M. (1, Wimpole Street, W.1.) Dr. Dwight Ingle: R of the Adrenal Cortex in Homeostasis.

MEDICAL SOCIETY OF LONDON, 11, Chandos Street, W.1
8.30 P.M. Pathological meeting.

MANCHESTER MEDICAL SOCIETY
5 P.M. (University of Manchester.) *Section of Odon* Mr. F. T. Monks: Study of the Innervation of the Developing Tooth-germ with Reference to the Innervat of Dentine.
9 P.M. *Section of General Practice.* Dr. C. E. S. Lynch: Pep Ulceration in General Practice.

Tuesday, 25th

ROYAL COLLEGE OF SURGEONS, Lincoln's Inn Fields, W.C.2
5 P.M. Mr. Cuthbert Dukes: *Familial Intestinal Polyp* (Hunterian lecture.)

ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W.1
5.30 P.M. *Section of Experimental Medicine.* Dr. W. L. James, Dr. C. N. Fletcher, Dr. J. C. Gilson: Diagnosis Pulmonary Emphysema.
8 P.M. *Section of Medicine.* Sir Henry Cohen, Dr. A. H. Robb-Smith, Dr. G. B. Dowling: Collagen Vascu Diseases.

INSTITUTE OF DERMATOLOGY, St. John's Hospital, Lisle Stre W.C.2
5.30 P.M. Prof. R. H. S. Thompson: *Enzymic Mechanisms* Skin.

WEST END HOSPITAL FOR NERVOUS DISEASES, 40, Marylebo Lane, W.1
5.30 P.M. Dr. Douglas Gordon: When the Electroencepha*graph Helps.*

Wednesday, 26th

ROYAL SOCIETY OF MEDICINE
5 P.M. *Section of Endocrinology.* Dr. Ingle: Experiment Diabetes.

ROYAL INSTITUTE OF PUBLIC HEALTH AND HYGIENE, 28, Portla Place, W.1
3.30 P.M. Miss Rosamond Caseley, F.D.S. R.C.S.: Malformatio and Irregularities of the Teeth and Jaws in Children.

INSTITUTE OF DERMATOLOGY
5.30 P.M. Dr. J. O. Oliver: Animal Parasites in Dermatology.

Thursday, 27th

ROYAL COLLEGE OF SURGEONS
5 P.M. Mr. T. Levitt: Status of Lymph Adenoid Goitre, Hashimoto's and Riedel's Disease. (Hunterian lecture.)

INSTITUTE OF CHILD HEALTH, The Hospital for Sick Children, Great Ormond Street, W.C.1
5 P.M. Prof. R. S. Pilcher: Surgery of Chest Disease.

INSTITUTE OF PSYCHIATRY, Maudsley Hospital, Denmark Hill, S.E.5
3 P.M. Prof. L. van der Horst (Amsterdam): Affective Epilepsy.

LONDON JEWISH HOSPITAL MEDICAL SOCIETY
8.30 P.M. (11, Chandos Street, W.1.) Prof. M. L. Rosenheim: Acute Nephritis.

ST. JOHN'S HOSPITAL DERMATOLOGICAL SOCIETY, 5, Lisle Street, W.C.2
4.15 P.M. Demonstration and discussion of clinical cases.

LIVERPOOL MEDICAL INSTITUTION, 114, Mount Pleasant, Liverpool, 3
8 P.M. Mr. R. H. Hannah: Cerebral Abscess.

Friday, 28th

POSTGRADUATE MEDICAL SCHOOL OF LONDON
2 P.M. (London School of Hygiene, Keppel Street, W.C.1.) Sir Geoffrey Jefferson, F.R.S.: Teaching Teachers. (First lecture in two-day conference-course on the Technique of Medical Teaching.)

ROYAL SOCIETY OF MEDICINE
5 P.M. *Section of Pædiatrics.* Dr. Brian Thompson, Mr. Dillw Thomas: The Fate of the Primary Complex.

INSTITUTE OF DERMATOLOGY
5.30 P.M. Dr. H. Gordon: Benign New Growths.

INSTITUTE OF DISEASES OF THE CHEST AND INSTITUTE OF CARDIOLOGY
5.30 P.M. (London School of Hygiene.) Dr. William Evans, Mr. Vernon C. Thompson: Constrictive Pericarditis.

INSTITUTE OF LARYNGOLOGY AND OTOLOGY, 330–332, Gray's Inn Road, W.C.1
4.30 P.M. Prof. F. C. Ormerod: *Cancer of the Larynx.*

MEDICAL SOCIETY FOR THE STUDY OF VENEREAL DISEASES, 11, Chandos Street, W.1
7.30 P.M. Dr. G. L. M. McElligott, Prof. W. D. Newcomb: Fatal Syphilis.

Saturday, 29th

LONDON ASSOCIATION OF THE MEDICAL WOMEN'S FEDERATION
2.30 P.M. (Middlesex Hospital, W.1.) Clinical meeting.

POSTGRADUATE COURSE ON RHEUMATIC DISEASES
10 A.M. (St. Stephen's Hospital, Fulham Road, S.W.10.) Sir Adolphe Abrahams: General Medicine in Relation to the Rheumatic Diseases. (Introductory address to week-end course.)

DISABLED IN THE MODERN WORLD.—Under this title the Central Council for the Care of Cripples has published the proceedings of the World Congress of the International Society for the Welfare of Cripples held in Stockholm last year. (Post-free 15*s.* 6*d.*, from the council, 34, Eccleston Square, London, S.W.1.)

THE SURGERY OF THE SPLEEN*

Sir Lionel Whitby
C.V.O., M.C., M.D. Camb., F.R.C.P.
GIUS PROFESSOR OF PHYSIC IN THE UNIVERSITY OF CAMBRIDGE

The surgery of the spleen and the various medical pects of splenectomy have been frequently and extenely reviewed in the past three years, and it is clear om all reports that splenectomy has come to be a atively common operation, providing effective, somenes dramatic, treatment for a number of medical nditions for which there neither was nor is any medical eatment. Extensive experience has now shown that, ve for a very few fairly well-defined risks and contradications, the operation per se has a very low mortality. rther, there is the comforting thought that, apart om the risks, even if removal of the spleen does no od at least it appears to do no harm.

It is this last fact which has led to the extension of lenectomy to the treatment of a number of diseases in hich perhaps its rationale is difficult to establish and e chance of clinical success, according to previous perience, may be quite small. One is inclined to take e chance if nothing else can be done to relieve perhaps n intolerable situation.

These general points raise some of the questions to hich we should like an answer. What are the functions f the spleen once it has ceased its fœtal function of ood production? What are the criteria for splenectomy, s judged by the disturbances and disorders of such nctions as are known? When is the operation certain o effect cure, and is the cure biological as well as clinical? hen is splenectomy a gamble, and what are the chances f clinical success?

Let us admit at once that the answers to some of ese questions are based on impression rather than stablished fact. I must naturally approach the subject om the point of view of a hæmatologist; for he, hether appreciated or not, is largely the arbiter and he dictator of the surgery of the spleen. Save for rauma it is not often that a spleen is removed without he hæmatologist having, not a finger in the pie, but a eedle in the vein or the sternum, or both.

FUNCTIONS OF THE SPLEEN

It is noticeable, from a study of the recent extensive eviews to which I have referred, that most of them quote alen's 1800-year-old aphorism that "the spleen is an rgan of mystery," as indeed it is. Nevertheless there eem to be three or four well-recognised actions of the spleen, even though we do not properly understand either the manner in which these operate, or their importance, or their significance in the physiology of the body, or their relation to the various pathological states for which splenectomy is successfully performed.

Thus, in the first place, the spleen, by reason of its peculiar anatomy with large venous sinuses, is known to be a reservoir for blood. This has at least some surgical implication, for it renders an injury dangerous and indicates the desirability of squeezing the splenic blood into the circulation before removing the organ. This may save a blood-transfusion.

Secondly, the histology of the spleen shows that it contains a large collection of lymphoid tissue with relatively more cells of the reticulo-endothelial system than any other organ in the body, and, because of the phagocytic activities of the cells of this system and because effete or abnormal red cells are foreign bodies, this aspect of splenic function may impinge upon pathology and hence surgery. In passing one should note that, if splenectomy is being performed because of destructive or phagocytic activities of the organ, it is important to search for and remove accessory spleens; otherwise the operation may be a failure.

Thirdly, the spleen is known to have a hæmopoietic function in the embryo and fœtus; but after birth (save in exceptional conditions which bring about compensatory myeloid metaplasia, when the enlarged spleen should not be removed because of simple hyperplasia), the spleen does no more than contribute a quota of lymphocytes and monocytes to the circulation.

There are, however, other and more subtle ways, embracing chemical or hormonal functions, disturbances of which may be successfully treated by splenectomy. I have used the adjective "subtle" because some of the functions at least seem quite unessential, and others have never been definitely proved to exist and have been deduced or suspected only because of the remarkably dramatic effect which removal of the spleen may exert, sometimes instantly, upon certain blood disorders.

HISTOLOGY

One might think that histological studies would reveal something specific and definite in some of the conditions for which splenectomy is beneficial and would indicate the nature of the deleterious influence which the spleen is exerting.

Unfortunately this is hardly ever the case, except for the conditions in which the spleen appears to over-exercise its zeal for phagocytosis. In these circumstances iron pigment, red cells, and the relics of leucocytes may be found in sections of the tissue, but there is always an uneasy feeling that the cells themselves have been at fault rather than the spleen. In congenital hæmolytic icterus, for example, where from the clinical results of operation the spleen must obviously be concerned, the histological picture is no more specific than the finding of small malpighian follicles, empty sinuses, and congested pulp, with a certain amount of free iron pigment. From the histological angle one can only make the general inference that in an organ of which the anatomy would permit sequestration and stagnation of cells in close proximity with tissue cells having well-marked phagocytic powers, as well as ability to produce antibodies of lytic type, excessive blood destruction may readily take place.

EXCESSIVE PHAGOCYTOSIS

We know that the spleen will ingest and destroy abnormal cells, since these are foreign to the circulation; and, though most work has been done on the red cells, it seems probable that leucocytes and platelets may be similarly selected for destruction by reason of abnormality. This is one aspect, though not the most important, of the concept known as hypersplenism.

What are the abnormal features of red cells which mark them down for selection and destruction by the spleen; and, more important from the aspect of the surgery of the spleen, what indication do these abnormalities give us about the probable result of splenectomy?

There are, in the first place, abnormalities of shape which in classical form are seen in the spherocytes of congenital hæmolytic icterus, the leptocytes and target cells of Mediterranean or Cooley's anæmia, and the sickle-cells of African anæmia. All of these alterations in shape may be directly observed with the microscope, or they may be indirectly inferred from the saline fragility test, since the thick cell of congenital icterus is, for physical reasons, unduly fragile, and the other two are the reverse.

The examples which I have given are all congenital diseases. But we know that similar changes in red cells can occur to some degree in acquired conditions. Thus even physiologically the spleen is known to increase the thickness of the red cells which pass through it, and splenectomy for a simple condition may cause the appearance of target cells in the circulation. And it is now well recognised that in hæmolytic anæmias of so-called acquired type the intensity of the active and operative hæmolysin may be sufficient to induce a well-marked spherocytosis.

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* A paper read in opening a discussion at the Medical Society of London on Jan. 28, 1952.

It is, however, *difficult to believe that cell shape* is a determining factor in producing a hæmolytic anæmia, since the anæmia may occur with either thick or thin cells. But one fact at least emerges—splenectomy is successful when cells are thick but useless, sometimes fatal, when cells are thin or sickled. And this general laboratory rule applies also to the acquired form of hæmolytic anæmia.

Modern work has perhaps opened a new line of approach towards the solution of these difficulties, since it has been shown that in some of the congenital defects, such as sickle-cell anæmia, the hæmoglobin *may* be in a form different from normal. In these circumstances it is easy to visualise a chain reaction whereby splenic function may become exaggerated not merely on a physical basis of thickness, shape, or size of a cell but also on the different chemical form of the hæmoglobin. At present, however, we cannot claim to know more than a fraction of the real picture of the hæmolytic anæmias. But there are certain clinical and laboratory facts which guide our judgment in advising splenectomy even though they do not explain the pathology.

Thus in *congenital hæmolytic icterus* we know that the cells are abnormal since they do not survive when transfused to a normal person, that the cells are spherocytic and therefore exhibit increased osmotic fragility, and usually, but *not always, no antibody of lytic type* can be demonstrated. We know that this disease can present with all grades of severity; that it can exhibit remissions and recrudescences; but that almost always there is evidence of constant blood destruction with active compensation, shown by a constantly high reticulocyte-count. We know that in the undoubted case splenectomy carries so little risk and promises so much benefit that I now never hesitate to advise the operation even with those whose symptoms are minimal. If left alone they are always liable to an acute crisis as the result of an infection or some other cause, and they have a constant risk of biliary tract involvement from pigment stones.

In the so-called *acquired hæmolytic icterus* it is recognised that the cells are normal but that they are subject to destruction by a circulating hæmolysin which can usually, but not always, be demonstrated indirectly by Coombs's test. Spherocytosis may be present and, when this is so, *splenectomy offers a good prospect of cure.* Otherwise it is preferable not to operate in an acute and febrile phase but to tide this over with transfusions, if it is found possible to obtain a donor whose cells are not sensitive to the patient's *hæmolysin.* In my own experience this has sometimes meant the examination of more than a hundred samples.

This form of hæmolytic anæmia, the acquired type, is thought, but not proven, to be due to hæmolysin arising, among other places, from splenic tissue; and this has a peculiarly potent opportunity in the splenic sinuses for the destruction of red cells. Splenectomy offers a bright but not absolute prospect of cure.

My most dramatic case of this type was that of a patient almost moribund on admission, with a hæmoglobin of about 3·5 g. per 100 ml., who made literally no response to transfusion other than the complication of hæmoglobinuria. But despite being in a very acute phase he never looked back once his spleen had been removed, which was done as a last desperate measure.

In both these types of hæmolytic anæmia the appears to be clinical rather than biological. congenital type retains the spherocytosis; the acq type usually retains a positive Coombs test.

Phagocytic activities leading to an anæmia hæmolytic features *may sometimes* be found as secondary phenomenon in some of the diseases in whi the spleen itself is involved. These include Hodgkin disease and other reticuloses, and Gaucher's disea In these circumstances splenectomy is justifiable and ma be symptomatically beneficial.

Apart, however, from actual lysis or phagocytosis red cells the spleen is believed to play a fundament part in certain types of refractory anæmia which ari by reason of splenic inhibition of marrow function.

This so-called hypersplenism which, in the case of r cells, may be combined with excessive phagocytos appears also to be capable of affecting leucocytes platelets. Hence the hæmatological states known panhæmatopenia, when all elements of the blood a concerned but each may be affected singly or combination.

The criteria for establishing *these states* are by means clear. But in practice there is no doubt th with an unexplained and intractable or refracto anæmia for which no treatment (other than repeat transfusion) is effective, the diagnosis must be serious considered.

INDICATIONS FOR SPLENECTOMY

In my own experience the cases which have respond to splenectomy either by a complete cure or by *prolongation of the intervals between transfusio* (sometimes with eventual cure) have all exhibited t paradox of an apparent aplastic anæmia, as judged the peripheral blood and a definite normoblastic hype plasia of the marrow. Splenectomy seems to allow relea of the marrow cells and restoration of marrow functio

A transfusion life is so burdensome, and a straigh forward splenectomy so free from risk, that I confe that I have little hesitation in recommending t operation in many cases of unexplained refracto anæmia with a gamble on success, even though t marrow does not show the changes I have just describe

Similarly with the chronic unexplained granulocyt penias, a certain but smaller proportion of succes can be expected; and the same is true of certa hæmorrhagic states with which the spleen is apparent concerned, since splenectomy may bring about comple and dramatic cure. This welcome result has long be known to follow in a proportion of cases of idiopath thrombocytopenic purpura. But the part played by t spleen in this disease has never been properly determine one school believing that the fault arises from hype splenism in the form of excessive destruction of platel *by the spleen, and another* in the form of sple inhibition of formation or release of platelets from th bone-marrow.

Neither of these views has yet led to the formulation of completely *reliable criteria* for estimating the likelihoo of success of splenectomy in curing the clinical stat This may well be because one purpuric state is much li another, and there is undoubtedly some difficulty i differentiating those purpuras which are *idiopathic*, splenic, in origin from those which have an allerg or an endocrine origin.

From the clinical angle, irrespective of theories speculation, it has been determined *that the acute form* of a disease with fever and toxæmia, but which have th laboratory criteria of thrombocytopenic purpura, carry considerable operative risk when splenectomy is per formed in the acute phase. But if such cases *can b* coaxed into a chronic state with blood-transfusion (an I am old-fashioned enough to believe that a pint *of reall* fresh blood, preferably almost by direct transfusion, i rth two or three pints of the preserved variety), then an eration done in the chronic phase is highly successful. Experience shows that the acute idiopathic condition ich arises at the menopause or at any other phase at ich an endocrine element might obviously be involved s a poor prognosis.

In effect what one really requires is a means of termining when a hæmorrhagic case is one of splenic rombocytopenia for which the operation of splenectomy n be regarded as offering an almost guaranteed prospect cure. So far as present knowledge goes, this evidence supplied by a definite Hess's test, an unequivocal duction in platelets—i.e., well below 100,000 per nm.—and a careful examination of the marrow, hich should reveal if not increased numbers at least asonable numbers of megakaryocytes which seem less ature than normal and exhibit little or no evidence of atelet formation.

In short, and perhaps more simply, if the platelets in rculation are grossly reduced and the marrow shows a rmal or excessive number of megakaryocytes, splenec- my can be undertaken with considerable confidence a successful result. The marrow picture is in principle osely comparable with that found in the refractory æmias of splenic origin.

Sometimes similar criteria may be found in purpuras hich are obviously secondary to reticuloses, to reticulo- rcoma, to Gaucher's disease, and in Banti's syndrome. n such circumstances splenectomy is justifiable since it ay relieve—indeed has a good chance of relieving— n unpleasant and worrying symptom; but it has no fect whatever on the primary disease.

I have not here attempted to cover all the vast field diseases for which splenectomy has been performed, to touch more than superficially upon the meaning of me of the tests upon which much prognostic or terminative reliance is placed.

But in conclusion I must just mention other splenic sorders in which the diagnosis may be established by e hæmatologist but in which the advisability of peration, and more especially the extent or type of peration, must rest entirely with the surgeon. I refer, course, mainly to Banti's syndrome, in which the nction of the hæmatologist is to exclude all other uses of splenic enlargement. I may perhaps add that y own experience of the results of simple splenectomy Banti's syndrome has been completely discouraging nd I imagine that the operation is now only performed s part of a bigger vascular readjustment.

Finally may I add a word of warning on a point hich I mentioned earlier. It is essential to examine the arrow before accepting a diagnosis of Banti's syndrome ccompanied by a large spleen. If the marrow is found be fibrotic from metastatic carcinoma or sclerosis of ny type, then it can be assumed that the splenic enlarge- ent is due to a resumption of hæmopoietic activity mpensating for the obliterated marrow. The removal the organ would then be a disaster.

"... Of course in the past, there were great catastrophes: for cample, plagues, floods, barbarian invasions. But, if such cata- rophes were warded off, there was a stable, well-known con- ition of civilised life. This assumption ... colours our political hilosophy and our educational theory, with their overwhelm- ig emphasis on past experience. The note of recurrence ominates the wisdom of the past, and still persists in many rms, even where explicitly the fallacy of its modern application admitted. The point is that in the past the time-span of portant change was considerably longer than that of a ngle life. Thus mankind was trained to adapt itself to fixed nditions.

"Today this time-span is considerably shorter than that of uman life, and accordingly our training must prepare dividuals to face a novelty of conditions."—A. N. WHITE- EAD. *Adventures of Ideas.* London: Pelican Series, 1951; . 114.

SPLENECTOMY: INDICATIONS AND TECHNIQUE*

RODNEY MAINGOT
F.R.C.S.
SURGEON, ROYAL FREE HOSPITAL, LONDON, AND SOUTHEND GENERAL HOSPITAL

IN recent years important advances have been made in the management of patients with surgical conditions of the spleen.

The advances have been mainly due to the excellent work of the hæmatologist, who has improved and enlarged the methods of diagnosis, expanded and rationalised the indications for splenectomy, and can now forecast, with a considerable degree of accuracy, the results following excision of the spleen for the splenopathies. It can be said that the results of splenectomy depend largely on the selection of cases by the hæmatologist.

The indications for splenectomy may be listed as follows:

I. SPLENECTOMY INDICATED

(1) Adjunct to other surgery—e.g., total gastrectomy for carcinoma of the stomach; œsophagogastrectomy for cancer of the cardia or lower end of the œsophagus; cancer of the tail and/or the body of the pancreas; certain cases of hyperinsulinism; cancer of the splenic flexure of the colon; &c.

(2) Ptosis of the spleen, or wandering spleen, with or without torsion of the pedicle of the spleen.

(3) Rupture of the spleen:
  (a) Penetrating wounds—e.g., gunshot wounds.
  (b) Non-penetrating (subcutaneous or closed) wounds due to blunt trauma to the left chest, abdomen, or left kidney region.
  (c) Spontaneous rupture of a normal or of a pathological spleen.
  (d) Operative injury—e.g., during partial gastrectomy.

(4) Congenital hæmolytic anæmia.

(5) Idiopathic or primary purpura hæmorrhagica.

(6) Idiopathic or primary splenic neutropenia.

(7) Idiopathic or primary panhæmatocytopenia.

(8) Cysts of the spleen:
  (a) Parasitic.
  (b) Non-parasitic: (i) solitary, (ii) multiple.

(9) Primary tumours—e.g., lymphosarcoma.

II. SPLENECTOMY MAY BE INDICATED

(1) Congestive splenomegaly (portal hypertension).

(2) Acquired hæmolytic anæmia.

(3) Secondary purpura hæmorrhagica.

(4) Secondary panhæmatocytopenia.

(5) Lymphoblastoma:
  (a) Giant lymph follicle hyperplasia.
  (b) Lymphosarcoma.

(6) Boeck's sarcoid.

(7) Tuberculosis of the spleen.

(8) "Egyptian" splenomegaly (schistosomiasis).

(9) Gaucher's disease.

(10) Splenomegaly of unknown origin.

Under the second heading, "Splenectomy may be Indicated" the most frequent and hopeful indications are congestive splenomegaly and acquired hæmolytic anæmia, and these will be discussed in some detail later. In the other conditions enumerated under this heading the principal reasons for advocating surgery are: (1) to rid the patient of the encumbrance occasioned by the presence of a large, weighty, and friable spleen; (2) to mitigate or arrest, for an unknown period, the evil effects of hypersplenism; (3) to forestall rupture of the organ; and (4) to excise an enlarged spleen of obscure ætiology in the hope that some cryptic process may be controlled.

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*Read before the Medical Society of London on Jan. 28, 1952.

SPLENECTOMY ADJUNCT TO OTHER SURGERY

In operations involving organs in close proximity to the spleen it is often necessary to do splenectomy.

For instance, in total (and in some cases partial) gastrectomy for malignant lesions of the stomach, the cardiac orifice, or the lower end of the œsophagus excision of the spleen simplifies the operation, reduces hæmorrhage, and at the same time renders the operation more radical, thus offering greater prospects of cure.

Carcinomas of the splenic flexure of the colon and of the tail or body of the pancreas require splenectomy along with removal of the primary growth.

During pancreatic resection for hyperinsulinism, the splenic vein is often irreparably damaged, and, when this happens, excision of the spleen becomes mandatory.

Splenectomy is also called for in cases of total pancreatectomy for carcinoma of the head (or body) of the pancreas, in some cases of diaphragmatic hernia, and where hæmorrhage from the splenic pulp cannot be staunched after a "rough-and-ready" partial or subtotal gastrectomy.

WANDERING SPLEEN

Wandering spleen is a rare abnormality. Few abdominal surgeons have operated on one or more cases of ptosis of the spleen. Up to now less than 150 cases have been reported.

The splenic attachments are such that little or any motion of the spleen takes place during respiration.

The causes of wandering spleen may be either (*a*) congenital, in which case the ectopic position of the spleen is due to an absence of the supporting phrenico-colic ligament; or (*b*) acquired as the result of trauma or splenomegaly.

In the acquired type the anchoring peritoneal folds or suspensory ligaments may become stretched and elongated. When the spleen becomes unduly mobile, pain is caused either by the drag on, or torsion of, the main vascular pedicle. Attacks of pain may recur for a long time, or a single irreducible torsion may produce a vascular occlusion and infarction of the viscus.

Splenectomy is the correct procedure for all cases of wandering spleen, whether complications are present or not, and is associated with an operative mortality of 0·5%.

Torsion of the spleen, of course, demands immediate operation to relieve the intense pain associated with infarction and to prevent the onset of serious intra-abdominal complications.

Splenopexy, for simple ptosis, which was originally done by Tuffier in 1882, is nowadays never done and is only of historical interest.

RUPTURE OF THE SPLEEN

Rupture of the spleen may be spontaneous or due to penetrating wounds (e.g., stabs and gunshot wounds); non-penetrating injuries due to trauma of the left chest, abdomen, or back; or surgical trauma during partial gastrectomy for peptic ulcer.

Spontaneous rupture may affect a normal or a pathological spleen. Rupture of a normal spleen is rare. Rupture of a pathological spleen occurs most commonly in malaria; typhoid fever; typhus; acute general infections; blood disorders, such as leukæmia; infectious mononucleosis; pregnancy, parturition, and the puerperium; and splenomegaly from any cause.

In all the conditions mentioned above the spontaneous rupture probably depends on some slight unnoticed trauma to the softened, toxic, congested, and diseased spleen.

Rupture of the spleen is stated to occur in 30–40% of all closed abdominal injuries (non-penetrating wounds). In a personal series of 10 cases (2 of which were associated with lacerations of the left kidney) there were 3 post-operative deaths. O'Connell (1951) and several other workers estimate the mortality at 30%.

If patients admitted to hospital with severe (and in some instance lethal) injuries are excluded, subcutaneous (closed) rupture of the spleen may be divided into two groups:

(1) *Considerable laceration of the spleen*, with abdominal pain, tenderness, and rigidity, either generalised or localised to the left upper quadrant, with features of shock and internal hæmorrhage, and with radiological evidence of crenation of the greater curvature of the stomach, downward displacement of the splenic flexure of the colon, and upward displacement of the left leaf of the diaphragm.

(2) *Small tears and subcapsular hæmatoma*, often followed from 2 days to 6 months later, by the symptoms and signs of delayed rupture—i.e., of internal hæmorrhage.

Delay in diagnosis, as O'Connell (1951) rightly emphasises, is the major factor responsible for the high mortality of ruptured spleen, although failure to deal with a concomitant injury to the left kidney accounts for a few fatalities.

Delay in diagnosis may often be traced to one or more of the following causes.

(1) Non-recognition of the possibility of trauma to the spleen owing to the trivial nature of the injury to the lower left chest, abdomen, or postrenal area.

(2) The apparent well-being of the patients when examined after the initial shock has subsided.

(3) The reliance for diagnosis of ruptured spleen on the recognition of the classical signs and symptoms of internal hæmorrhage. It should be noted here that the so-called classical clinical picture of internal hæmorrhage, which is described in many textbooks of surgery and medicine, is that of the final phase when death is approaching.

(4) The absence of Kehr's sign or the failure to recognise this valuable sign. Kehr's sign is present in only about 10% of cases in the early hours after injury to the spleen.

O'Connell (1951) suggests that before pronouncing that this sign is negative in suspicious cases, and as a method of diagnosis, the patient should be asked to lie down flat with the end of the bed raised on blocks. If there is free blood in the abdominal cavity, the patient will complain of shoulder-tip pain within a few minutes. As soon as the diagnosis of rupture is established, blood-transfusions should be given to replace the blood which has been lost, the abdomen should be opened through a left paramedian incision, and, after expeditious excision of the lacerated spleen, the left kidney should be carefully examined by sight and touch. The operation is completed by a rapid exploration of the other abdominal viscera, the removal of large blood-clots, and secure closure of the various layers of the wound.

HÆMOLYTIC ANÆMIA

There are many causes of "hæmolytic anæmia," and the surgeon depends on the hæmatologist to exclude those types in which the normal red cells are hæmolysed by malignant disease, certain drugs, pyogenic or protozoal infections, the reticuloses, and so forth.

The primary hæmolytic anæmias are divided into congenital and acquired types.

Congenital Hæmolytic Anæmia

The congenital type is diagnosed by its familial incidence, the presence of splenomegaly associated with anæmia, reticulocytosis, spherical microcytes (spherocytosis), increased fragility of the erythrocytes, elevated serum-bilirubin level, "crises" with bouts of jaundice, and the fact that the Coombs test is often negative. In this disease, which was first described by Minkowski

.900), a strong family history is almost invariably icited, and it is agreed that the condition is transmitted s a mendelian dominant character.

In congenital hæmolytic anæmia the disease may be iscovered at any age; the degree of jaundice varies ut is proportional to the degree of anæmia; the per-entage of reticulocytes in the peripheral blood also aries within wide limits depending on the severity of he hæmolytic process; small pigment stones form n the biliary passages in about half the cases; Coombs's est is usually negative but may be positive during severe crisis; and biopsy of the bone-marrow helps n the diagnosis because spherocytes are found in the marrow and the erythroid precursors predominate onspicuously over the myeloid.

The treatment is splenectomy, combined with removal of an accessory spleen or spleens (which are present in about a third of the cases), and with exploration of the gall-bladder, and bile-ducts for pigment stones or gravel. If the patient's condition is satisfactory, and gall-stones are present, splenectomy combined with cholecystectomy and T-tube choledochostomy should be carried out either through a lengthy left paramedian ncision or a transverse epigastric muscle-cutting ncision.

The added procedures of excision of the gall-gladder and choledochostomy do not increase the operative risks, provided the patient is fit, the anæmia mild, and the jaundice slight. If, however, the patient is debilitated as the result of a severe hæmolytic activity, it is advisable to do splenectomy first, and to deal with the gall-stones and sediment in the extrahepatic ducts by cholecystectomy and T-tube choledochostomy some weeks later.

The results of splenectomy for congenital hæmolytic anæmia are excellent; the operative mortality is less than 1%; jaundice speedily vanishes, anæmia is cured, and good health is maintained. Spherocytosis persists, and the "fragility" remains unaltered.

If in a case of congenital hæmolytic anæmia there is a recurrence of the pristine signs and symptoms, the implication should be clear and the treatment obvious.

A recurrence implies one thing only—an accessory spleen was not detected at the primary operation, and with the passage of time this sinister structure has grown in stature and assumed the form and even the "viciousness" of its departed forebear.

In a personal series of 18 splenectomies there were no operative deaths, an accessory spleen (or spleens) was found in 6 instances, pigment stones were encountered in only 3 cases, and the late results were uniformly satisfactory. In the 3 patients with gall-stones splenectomy was combined with excision of the gall-bladder and exploration of the bile-ducts.

In this disease gall-stones are rarely encountered in children and adolescents; they are most commonly found in patients over the age of 45.

Acquired Hæmolytic Anæmia

In acquired hæmolytic anæmia splenomegaly is associated with anæmia, jaundice is usually present, spherical microcytes are rarely seen in the peripheral blood, the red-cell fragility is usually normal, and the Coombs test is positive. A familial history is absent.

DIFFERENTIAL DIAGNOSIS OF PRIMARY HÆMOLYTIC ANÆMIA

—	Congenital	Acquired
Familial history	Present	Absent
Splenomegaly	Present	Present
Hæmoglobin and red cells	Anæmia	Anæmia
Reticulocytes	Increased	Increased
Serum-bilirubin level	Raised	Raised
Spherical microcytes	Present	Absent
Red-cell fragility	Increased	Normal
Coombs's test	Negative	Positive
Splenectomy	Excellent results	Poor results

The essential points in the differential diagnosis of the congenital and acquired types of hæmolytic icterus are given in the accompanying table.

In my experience the rôle of surgery in acquired hæmolytic icterus is discouraging, fully 70% of the patients being unaffected by removal of the spleen.

I am aware that Learmonth (1951) estimates that splenectomy is effective in about half the cases, and that this view is shared by other workers. Rousselot (1949), however, states: "Our experience has been generally disappointing in this group. Surgery offers very little more than a 15% chance of arrest of the hæmolytic activity, with 85% unaffected by removal of the spleen."

Whereas the diagnosis of the congenital type can often be made with confidence, the same cannot be said of the acquired type, which has to be differentiated from a host of conditions capable of producing hæmolytic anæmia, including drug idiosyncrasy, lymphadenoma, lymphosarcoma, Cooley's anæmia, pyogenic infection, &c.

Medical therapy is obviously called for whenever the responsible mechanism is capable of being arrested or cured. In the primary form of acquired hæmolytic anæmia the mainstay of medical treatment is blood-transfusion. When repeated transfusions are ineffective in maintaining an adequate blood level, or are complicated by severe hæmolytic crises, then, and only then, should splenectomy be entertained.

It is the occasional success following splenectomy which sustains the surgeon's interest in this baffling disease.

PRIMARY OR IDIOPATHIC THROMBOCYTOPENIC PURPURA HÆMORRHAGICA

In some 90% of instances in which it is encountered, purpura represents a symptom-complex rather than a disease.

It may appear in the course of many common ailments, and when it does so it is referred to as secondary or symptomatic purpura.

The terms "primary," "essential," and "idiopathic" are reserved for those cases in which no associated disease or cause for the symptom-complex can be found.

Secondary Purpura

The secondary purpuras, then, are those for which there is thought to be an assignable cause.

They are the purpuras which occur with infections, poisoning by toxic agents, nutritional deficiencies, allergic states, and certain diseases of the spleen, such as the reticuloses, Boeck's sarcoid, lymphoblastoma, leukæmia, secondary panhæmatocytopenia, &c.

In the secondary purpuras treatment should be directed at the disease causing the purpura.

Splenectomy in this group is, in my opinion, emphatically contra-indicated, and is often attended by tragic consequences.

It is often stated that splenectomy should be done in selected cases of secondary purpura to relieve the damaging effects of associated hypersplenism, and that the late results are satisfactory. In my experience, however, the "satisfactory results" are attributed to the fortuitous discovery during convalescence of an "assignable cause" of the purpura and to the appropriate treatment thereof rather than to splenectomy.

Primary or Idiopathic Purpura

Primary purpura can only be diagnosed by the exclusion of all factors known to cause purpura. It may be defined as an idiopathic hæmorrhagic disease characterised by bleeding from the mucosæ, petechiæ, ecchymoses, secondary anæmia, reduction in the number of platelets (80,000 or less per c.mm.), and prolonged bleeding-time.

The condition is four times commoner in females than in males, and, although it occurs most often in childhood and early adult life, no age is exempt. Its pathogenesis is unknown, although those who believe in "hypersplenism" assert that the spleen exercises a primary rôle in selective sequestration of the platelets.

There are two forms of primary purpura: the chronic or relapsing, which is, as a rule, easy to recognise; and the acute or fulminating, which is difficult to diagnose with exactitude. In the latter group splenectomy is a life-saving surgical emergency, and is an imperative procedure to prevent fatal blood-loss, or irreparable damage to the brain, retina, liver, or kidney.

The results have shown that splenectomy, plus removal of accessory spleens when present, offers a greater hope of complete arrest of idiopathic purpura than any other form of treatment.

The results following splenectomy are good, 70–75% of the patients being cured, and the operative mortality being low. Elliott and Turner (1951) report a series of 69 splenectomies for primary purpura without a fatality, and with 72% satisfactory results; Lahey (1948) recorded 17 cases with no operative mortality and 75% cures; and I have operated on 23 cases (4 acute and 19 chronic) with one fatality and with gratifying results in over two-thirds of the cases.

The age of the patient and the size of the spleen influence the prognosis. The older the patient the worse is the prognosis. In my series the poor results were observed in patients with "sizeable" spleens.

Experience leads me to believe that in the idiopathic type of purpura the spleen is not enlarged, that it is normal in weight and structure, and that accessory spleens are found in fully 30% of the cases. Some so-called "recurrences" are unquestionably due to overlooking an accessory spleen during splenectomy.

ACCESSORY SPLEENS

In doing a splenectomy a careful search should be made for accessory spleens. These are most often found in the gastro-splenic omentum, near the hilum anterior to the main splenic vessels, in the great omentum, near the tail of the pancreas, in the pancreatico-splenic ligament, and in the intestinal mesenteries. Accessory splenic tissue is *occasionally found in the left ovary or in the left testicle.*

An accessory spleen is present in 15–35% of all necropsies.

In a personal series of 100 consecutive partial or subtotal gastrectomies for chronic peptic ulcer an accessory spleen was found in the gastrosplenic omentum or in the great omentum in 13 cases. In splenic diseases they are encountered frequently. Curtis and White (1936) in the course of 35 splenectomies observed accessory spleens in 7 instances (20%). This subject receives the expert consideration of Settle (1940) and Curtis and Movitz (1946).

Except when operating for rupture, I have always made a point of searching for an accessory spleen in all cases in which I have done splenectomy. In 23 consecutive cases of splenectomy for idiopathic purpura I found one or more accessory spleens in 8 cases.

Accessory spleens are present in about 30% of cases of familial hæmolytic anæmia. The last patient on whom I operated for this disease, a boy aged 12 years, had two large accessory spleens in the splenocolic ligament and a small one in the gastrosplenic omentum.

Where splenectomy is indicated and an accessory spleen is discovered at operation, it should be excised in all cases, except where the spleen is being removed because of rupture, because these tissues undergo a further maleficent hypertrophy and cause a continuance of the morbid condition for which the splenecto undertaken.

Splenosis is a different condition from a spleens, and consists of small clumps of splenic scattered throughout the peritoneal cavity. It re from the implantation of minute fragments of tissue disseminated by blood after rupture, or of the splenic pulp during splenectomy.

CONGESTIVE SPLENOMEGALY: PORTAL HYPERTENSIO

Nowadays the terms "splenic *anæmia*," "Bant disease," and "Banti's syndrome" have been supersed by the newer and more *descriptive terms* "congesti splenomegaly" and "portal hypertension."

The pathogenesis of this syndrome is portal bed blo with concomitant portal hypertension. The obstructi *in the portal bed may be intrahepatic or extrahepat* The site and type of lesion capable of producing congesti *splenomegaly can be classified as follows:*

I. INTRAHEPATIC BLOCK

Cirrhosis of Liver:

(1) Laennec cirrhosis.
(2) Schistosomiasis.
(3) Biliary cirrhosis.
(4) Infectious hepatitis.

II. EXTRAHEPATIC BLOCK

(1) *Stenosis of Portal or Splenic Vein:*
  (*a*) Congenital.
  (*b*) Acquired.
(2) *Compression of Vein:*
  (*a*) Inflammatory cicatrix (following pancreatit cholangitis, &c.).
  (*b*) Pancreatic cyst.
  (*c*) Tumours.
  (*d*) Aneurysm of splenic artery.
(3) *Thrombosis of Portal or Splenic Vein:*
  (*a*) Inflammatory.
  (*b*) Traumatic.

The clinical picture and the blood findings vary accor ing to the site and nature of the block.

Asthenia, splenomegaly, pallor, leucopenia, thromb cytopenia, and anæmia are observed in all the cas The frequent and dreaded symptom of hæmatemes occurs irrespective of the site of the obstruction. Jaundi and ascites are evident when advanced cirrhosis of t *liver is present.*

The following facts should be noted:

(1) When the block is extrahepatic, the liver usual appears normal.

(2) In 20–25% of cases of severe hepatic cirrhosis splen megaly is absent.

(3) In some cases portal obstruction *cannot be demonstrate*

(4) From splenectomy alone no beneficial effects up the ascites are derived, *but an associated hypersplenis* is temporarily cured in about 80% of the cases.

Banti advised splenectomy in the "first stage" of th disease—"splenic anæmia." Thus splenectomy ha remained the basic operation until the work of Whi (1945), Blakemore (1948), and their co-workers in America, and Hunt (1952) and Learmonth (1951) in this country.

The results of splenectomy alone were variable. Many patients with congestive splenomegaly and associated gastro-intestinal bleeding had excellent results, with cessation of the hæmorrhages, following splenectomy alone when the block was close to the spleen.

On the other hand, when the block was intrahepati or close to the porta hepatis, splenectomy had little or no effect upon the bouts of hæmatemesis and/or melæna; in fact, most of the patients in this group eventually died of hæmorrhage.

Since splenectomy alone could not be relied on to prevent recurrence of hæmorrhage, especially in those ses where the block was intrahepatic, additional rgical measures had to be devised.

The ultimate prognosis and the selection of the type f surgical therapy in any given case of portal hypernsion will depend on: (1) the nature of the obstructive ctor, (2) its position, (3) the degree of portal hypernsion, and (4) the efficacy of the collateral circulation.

In the absence of gross irreversible hepatic and/or nal damage, in fact in the cases that are deemed worthy f operation, the following procedures have been ttempted to arrest bleeding from œsophageal varices nd from the mucosa of the gastro-intestinal tract:

(1) Injection of sclerosing solutions into the varices.
(2) Ligation of the veins about the cardia.
(3) Œsophagogastrectomy combined with splenectomy nd with spleno-renal anastomosis.
(4) Packing the superior mediastinum.
(5) Splenectomy followed by spleno-renal anastomosis r portacaval shunt.

In the light of our present knowledge it is felt that he operation of choice is splenectomy followed by nd-to-side spleno-renal anastomosis or side-to-side ortacaval anastomosis by the suture method.

It is as yet difficult to assess the late results, but he published figures of Whipple (1945), Blakemore 1948), Linton et al. (1948), Hunt (1952), and others are, n the whole, encouraging.

In attempts to alleviate, correct, or cure a complicated nd lethal pathological state these and other surgeons ave shown courage, determination, and technical skill orthy of the highest praise.

HYPERSPLENISM

Doan (1945) and Dameshek and Miller (1946) have escribed what they believe to be a clinical entity and ave called "hypersplenism." Hypersplenism is a unctional disturbance and not a specific pathological ntity.

The "sequestration" theory of Doan involves the phagocytosis of one or more of the cellular elements of the blood by the spleen. Thus, the phagocytosis of large numbers of erythrocytes leads to hæmolytic anæmia; of leucocytes to neutropenia; of platelets to primary or idiopathic purpura; and of all three cellular elements of the blood to panhæmatocytopenia.

In splenectomy for the primary or idiopathic forms of these diseases we remove a focus of disease, in fact a parasitic organ. The spleen has a vicious, perverted, or vicarious appetite either for red cells, white cells, or platelets; or, again, it may display an avidity for all these cells which circulate in the splenic pulp.

As an alternative hypothesis, Dameshek holds that the spleen normally exerts a hormonal inhibitory action on bone-marrow blood formation. If this inhibitory action is exaggerated, depression of one or more of the cellular elements and hypersplenism may occur.

The so-called primary forms include splenic neutropenia, with or without thrombocytopenia; splenic panhæmatocytopenia with non-hæmolytic anæmia; and, lastly, splenic panhæmatocytopenia with hæmolytic anæmia.

Hypersplenism and these cytopenias may be associated with a variety of known causes, such as Gaucher's disease, cirrhosis of the liver, Hodgkin's disease, lymphosarcoma, syphilis, kala-azar, tuberculosis of the spleen, Boeck's sarcoid, and malaria.

In the primary forms of hypersplenism splenectomy is beneficial, but in the secondary types it offers little else but a temporary palliation.

TECHNIQUE OF SPLENECTOMY

The incision of choice depends on the nature of the disease. Thus, in the "primary hypersplenisms" and in rupture, a lengthy left paramedian incision, with outward dislocation of the rectus muscle, is adequate; in congenital hæmolytic anæmia a transverse epigastric incision which permits exploration of the biliary tract affords excellent exposure; and in congestive splenomegaly a combined abdomino-thoracic incision, with partial division of the diaphragm, is indicated owing to the tethering adhesions which are so often encountered.

Splenectomy is simple, safe, bloodless, and expeditious in most of the surgical conditions of the spleen. The operative mortality is low, and postoperative complications are rare.

In congestive splenomegaly, however, the technical difficulties are considerable owing to binding adhesions, hæmorrhage is brisk, splenectomy is tedious and exacting, and the shunting of the portal blood into the caval system demands the construction of a neat, watertight, and impeccable anastomosis between two veins.

Splenectomy is done by dividing the blood-vessels in the gastrosplenic omentum, and, after the spleen has been mobilised and delivered through the wound and the tail of the pancreas has been freed, the main splenic vessels are individually ligated and divided, or they may be clamped, severed, and tied with strong silk after the three-clamp method of Féderoff.

SUMMARY

The basic operation in surgical disorders of the spleen is splenectomy.

A search should always be made for accessory spleens, which should always be removed whenever they are found. In the "primary hypersplenisms" an overlooked accessory spleen may grow in stature and reproduce the disease—e.g., idiopathic purpura—for which the primary splenectomy was undertaken.

The incisions of choice are left paramedian, transverse epigastric, and combined abdomino-thoracic. The combined incision is indicated in portal hypertension.

The operative mortality of splenectomy is low, and the late results are excellent in ptosis, primary purpura, congenital hæmolytic anæmia, primary splenic neutropenia, idiopathic panhæmatocytopenia, and cases of cysts of the spleen.

In hypersplenism and in those cytopenias due to a variety of *known* causes, the operative mortality is low but the late results are disappointing.

In most cases of portal hypertension splenectomy should be combined with spleno-renal or portacaval anastomosis. The operative mortality remains high. This is in part due to the nature of the disease, faulty selection of cases, and imperfections in the technique of vascular surgery. In the hands of the experienced surgeon who has made a special study of portal hypertension the results in selected cases are promising.

Finally, it may be justly said that in the splenopathies surgery will always be an important weapon of research and inquiry, and that the hæmatologist and the surgeon working in the closest union can solve many of the problems associated with splenic disorders.

REFERENCES

Blakemore, A. H. (1948) *Ann. Surg.* 128, 825.
Curtis, G. M., Movitz, D. (1946) *Ibid*, 123, 276.
— White, P. L. (1936) *Trans. Surg. Ass.* p. 364.
Dameshek, W., Miller, E. B. (1946) *Blood*, 1, 27.
Doan, C. A. (1945) *J. Lab. clin. Med.* 30, 385.
Elliott, R. H. E. jun., Turner, J. C. (1951) *Surg. Gynec. Obstet.* 92, 539.
Hunt, A. (1952) Hunterian lecture on "Surgical Treatment of Banti's Syndrome."
Lahey, F. H. (1948) *Ann. Surg.* 128, 363.
Learmonth, J. (1951) *Brit. med. J.* ii, 67.
Linton, R. R., Hardy, I. B. jun., Volwiler, W. (1948) *Surg. Gynec. Obstet.* 87, 129.
Minkowski, O. (1900) *Kersh. Kongr. Inn. Med.* 18, 316.
O'Connell, T. C. J. (1951) *Brit. med. J.* ii, 1404.
Rousselot, L. M. (1949) *Surg. Clin. N. Amer.* p. 369.
Settle, E. B. (1940) *Amer. J. Surg.* 50, 22.
Whipple, A. O. (1945) *Ann. Surg.* 122, 449.

INCIDENCE AND MECHANISM OF THE EARLY DUMPING SYNDROME AFTER GASTRECTOMY

A CLINICAL AND RADIOLOGICAL STUDY

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THE operative mortality of subtotal gastrectomy for peptic ulcer in experienced hands is now small—not more than 2–3%—and the risk of recurrent ulceration is slight. The excellence of these results, however, is offset by the fact that some of the patients develop the so-called post-gastrectomy syndromes. These comprise bilious regurgitation, loss of weight, steatorrhœa, diarrhœa, vitamin deficiencies, and—most frequent and troublesome of all—a sense of epigastric fullness coming on during, or soon after, a meal and sometimes associated with faintness. This last symptom has been termed the dumping syndrome because it was originally believed to be due to the precipitate passage of food from the stomach into the jejunum, which was thus forcibly distended (Hurst 1913, Mix 1922).

Dumping is very common after high gastrectomy, and in our experience few patients in the early stages after this operation are entirely free from it; but it is usually mild and can be obviated by restricting the size of meals taken to three-quarters or a half of those taken before the operation. In six to twelve months, moreover, the patients find that their capacity to cope with larger meals without discomfort gradually increases. In some 10–15% of the cases, however, the dumping syndrome becomes severe and disabling, and these patients are so overcome by the epigastric discomfort and associated symptoms, such as lassitude, nausea and flatulence, cold sweating, flushing of the head and face, and even syncopal attacks, that they have to lie down for half an hour or so after meals.

MECHANISM OF DUMPING

There has been much discussion about the mechanism of "dumping." The related vasomotor and general symptoms, such as faintness and sweating, in severe cases has suggested to Barnes (1947) and Gilbert and Dunlop (1947) that the "dumping" may be due to the transient hypoglycæmia which has been observed soon after the ingestion of food in many patients who have undergone gastrectomy. But according to Irvine (1948), Muir (1949), and Machella (1949, 1950) this hypoglycæmia does not occur till an hour or more after eating. Hence, though it may possibly explain occasional late postprandial symptoms in some cases, it clearly cannot be responsible for the early dumping syndrome, which is regularly experienced within a few minutes or half an hour of taking food. Other causal factors must be sought for this.

The theory of Hurst (1913) and Mix (1922) is supported by Muir (1949) and Machella (1949, 1950), who in gastrectomy cases reproduced the sensation of epigastric fullness, and sometimes even the associated vasomotor symptoms, by distending the distal or efferent limb of the jejunum by means of an inflatable balloon.

Other workers (Ogilvie 1935, Maingot 1948, Mimpriss and Birt 1948) suggest that dumping arises from reflux distension of the proximal jejunal loop and duodenum. And, finally, though the gastric remnant usually empties rapidly after gastrectomy, in some cases delayed emptying of the stomach (Mimpriss and Birt 1948) has been claimed as the cause of dumping symptoms. Indeed, Butler and Capper (1951) believe that stretching of the gastric stump is the commonest cause of dumping after gastrectomy.

Ogilvie (1935), Maingot (1945, 1948), Barnes (194 Gilbert and Dunlop (1947), Mimpriss and Birt (194 Porter and Claman (1949), O'Neill (1950), Capper Butler (1951), and other workers claim that the incide of dumping can be influenced by the type of operation. It seems to us, however, that the efficacy of the different types in this respect has been assessed in too partisan a spirit and that there is a need for more impartial analyses of their worth. Accordingly we here present some clinical and radiological observations on the incidence and mechanism of dumping in 224 patients subjected to various forms of partial or total gastrectomy for gastric or duodenal ulcer or carcinoma ventriculi. This series, treated by one of us, was consecutive except that it omits 11 patients who died of the operation and 7 who could not be traced or showed early signs of recurrence of carcinoma and were therefore unsuitable for investigation.

In view of the natural tendency for dumping symptoms to improve spontaneously, it was considered essential for fair comparison of different groups of patients to investigate them at about the same interval after operation in all cases. We chose arbitrarily to make this interval six months. Usually our clinical assessment was made on the basis of a special interrogation and examination in the outpatient department, but in a few cases the information had to be obtained by post. Ideally each patient would also have been submitted to radiography of the upper gastro-intestinal tract at the same time, but the labour involved was prohibitive, and only a proportion in each group were investigated radiologically. These patients were selected as a consecutive series of, say, the first 25 or 30 treated by that particular operation and are, we believe, a fair sample of the whole group having that operation.

TYPES OF OPERATION

According to the extent of the resection the operations were classified into three groups:

Subtotal Gastrectomies

This, the largest, group comprised 158 cases, in which about from three-quarters to four-fifths of the stomach was removed, the small gastric stump being nourished by only two or three short gastric arteries. The distal line of section was always taken beyond the pyloroduodenal junction and, in the case of duodenal ulcers, invariably beyond the ulcer. The operation was then completed in 45 cases by the *Billroth I technique* with gastroduodenal approximation (fig. 1*a*), in 60 cases by the *Moynihan antecolic modification of the Polya technique* (fig. 1*b*), and in 53 cases by the *antecolic Hofmeister-Finsterer* method (fig. 1c). In 12 cases of this last group with closure of the upper part of the cross-section of stomach the valve was made so large that the remaining stoma was only 1 in. wide, as suggested by Porter and Claman (1949).

Low Partial Gastrectomies

52 cases were treated by a lower gastrectomy, taking away only the distal half, or sometimes two-thirds, of the stomach, the gastric remnant being supplied by *all the short gastric* arteries and occasionally the left gastro-epiploic vessels as well. The operation ended with closure of the duodenal stump and the establishment of an end-to-side gastrojejunostomy by the antecolic Polya-Moynihan technique (fig. 1*d*).

Total Gastrectomies

In 14 cases the entire stomach was removed with the lowermost inch of œsophagus and usually also with the spleen and most of the body of the pancreas. Continuity was restored by closing the duodenal stump and establishing an œsophagojejunostomy. In 5 cases this consisted of a simple end-to-side anastomosis between the œsophagus and a jejunal loop, with subsequent entero-anastomosis (fig. 1e). In 9 cases the Roux manœuvre was adopted (*fig. 1f*) with end-to-end œsophagojejunostomy and end-to-side jejunojejunostomy. Some of these operations were *done entirely* through the abdomen, others by an abdomino-thoracic approach.

Radiological Observations

echnique

No special preparation was made other than asking he patient to abstain from food and liquids by mouth or ten hours before the examination. A proprietary rand of barium meal, 'Micropaque,' was used. One uid ounce of the undiluted meal was given first to study he mucosal pattern of the stomach remnant and ejunum and the immediate distribution of the barium etween the afferent and efferent limbs of the jejunal oop. It was found advantageous at this stage to xamine the patient in a true postero-anterior position, nstead of the routine right anterior oblique position, to btain a better view of the first filling of the jejunum. fter inspection of the mucosal patterns under the uorescent screen and after the necessary radiographs ad been taken, the patient was given a further four uid ounces of 50% diluted barium preparation and xamined in the erect, supine, and prone positions.

All the patients were seen a second time after an nterval of an hour to assess the emptying-time of the astric loculus and the state of filling of the jejunum and uodenum.

illroth I Gastrectomies (21 cases)

The first mouthfuls of the barium meal were not tained at all in the stomach but passed immediately nto the duodenum and within a few minutes had entered he upper coils of jejunum. The remainder of the meal as similarly quickly disposed of, and in 18 of the 21 ases the entire meal had left the stomach, except for ight mucosal smearing, in five to ten minutes. In 20 ases the stomach was completely empty on repeat xamination after an interval of an hour.

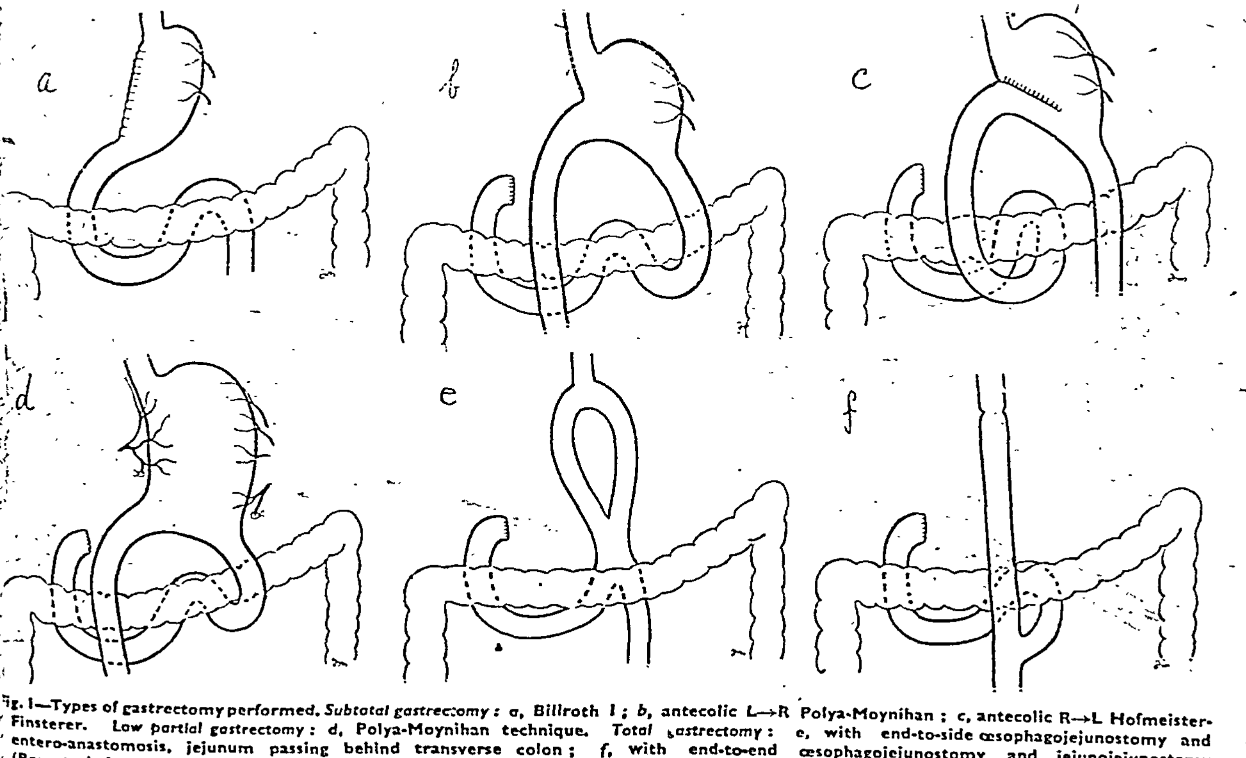
The only retention of barium mixture noted in the omach was when the duodenal loop and upper jejunum ad been completely filled, with the result that temorarily the final portion of the meal had to be accommodated in the gastric remnant (fig. 2). The third portion of the duodenum was often dilated and unduly dependent as if from acting as a second stomach; occasionally the upper jejunal coils seemed slightly dilated. Other notable features were the small size of the gastric remnant and its position high up under the left cupola of the diaphragm, the first and second parts of the duodenum being drawn over to the left by it. The edge representing the closed upper part of the cross-section of stomach was often irregular, simulating an ulcer crater or recurrent carcinoma.

Polya-Moynihan Gastrectomies (20 cases)

In 18 cases there was no immediate retention of barium in the stomach; instead it escaped directly into the jejunum. In 1 case the meal entered only the distal or efferent limb of jejunum, but in 14 both afferent and efferent limbs were filled, and in many cases the afferent limb was outlined as far as the duodenal stump (fig. 3). Only when the jejunum was well filled did the stomach stump become distended with barium. In these circumstances pronounced bulging of the jejunum opposite the stoma, as described by Kennedy et al. (1947), was noted in 6 cases. Some dilatation of the proximal and distal limbs of the jejunum was also observed in 5 cases.

Hofmeister-Finsterer Gastrectomies (20 cases)

In only 3 cases was there any initial retention of barium in the stomach; in all the others the meal passed immediately into the jejunum. In 6 cases the barium entered the afferent limb and filled as far as the duodenojejunal junction or even to the duodenal stump (fig. 4), but in the remaining 14 cases the afferent limb was not filled or was filled only to the top of the valve (figs. 5 and 6). The jejunum showed some evidence of dilatation in 4 cases. In 14 cases also, contrary to the findings of Porter and Claman (1949), there was some gastric dilatation opposite the stoma and valve (fig. 6). In 17 cases the stomach was empty, except for mucosal smearing, in an hour.



ig. 1—Types of gastrectomy performed. *Subtotal gastrectomy: a,* Billroth I; *b,* antecolic L→R Polya-Moynihan; *c,* antecolic R→L Hofmeister-Finsterer. *Low partial gastrectomy: d,* Polya-Moynihan technique. *Total gastrectomy: e,* with end-to-side œsophagojejunostomy and entero-anastomosis, jejunum passing behind transverse colon; *f,* with end-to-end œsophagojejunostomy and jejunojejunostomy (Roux technique), jejunum again proceeding behind transverse colon.

Hofmeister-Finsterer Gastrectomies with Specially Small Stoma (6 cases)

Radiologically there was no striking difference between these cases and those treated by the conventional Hofmeister-Finsterer operation. In all of them the barium started to flow immediately into the jejunum, and repeat radiographs after one hour showed the stomach to be empty except for mucosal smearing in all cases. The proximal limb was filled to a well-marked extent in only 1 case.

Total Gastrectomies (8 cases)

Radiologically 4 cases in which the œsophagojejunal anastomosis was completed by the simple loop method with entero-anastomosis all showed immediate flooding of both the jejunal limbs and filling of the duodenum. The upper jejunum was definitely dilated (fig. 7) in 3 cases. In 2 of 4 cases completed by the Roux method barium was seen radiologically to enter the side jejunal limb and fill the duodenal stump in addition to the main limb of the jejunum (fig. 8). Jejunal dilatation was noted in 3 cases.

SUMMARY OF RADIOLOGICAL FINDINGS

Emptying of Stomach Stump

The first striking feature is that after all forms of distal subtotal gastrectomy—in which the pyloric sphincter is sacrificed—the stomach remnant loses its power of active retention of food. Consequently food passes immediately under the influence of gravity from the stomach into the duodenum or into the upper jejunum, if they can accommodate it. Only if the intestine is already filled to capacity as in the later stages of a meal, does food remain temporarily in the stomach. In these circumstances the weight of the meal is still borne by the intestine, but the distension of the small gastric remnant is perhaps valuable in increasing the capacity of the upper gastro-intestinal tract for food, and in enabling the patient to take a larger meal than would be possible if the entire stomach had been removed.

The immediate emptying of the stomach stump was not surprising after the Polya type of gastrectomy with wide stoma, but it was contrary to what one had been led to expect by Morley and Roberts (1928), Ogilvie (1935), Lake (1948), and particularly Shanks (1934) for gastrectomies of Billroth I or Hofmeister-Finsterer type with restricted stoma. In either of these operations, practised by us, the upper three-quarters at least of cross-section of stomach is closed, and only a gastric stoma is left. In the Billroth I resections gastric stoma is slightly smaller than the lumen of duodenum into which it opens, owing to the narro produced by the infolding during suturing. Yet extre rapid emptying, normally within four or five minutes was the rule after this form of resection. It therefore seems that, though the normal configuration of the gastroduodenal apparatus is to some extent maintained by this technique and food enters the jejunum via the duodenum, the Billroth I gastrectomy is not, as Morley and Roberts (1928) supposed, a much more physiological procedure than the Polya type of operation. (Incidentally, even if it were, this might not be a genuine advantage; for it could reasonably be argued that the main object of surgery for peptic ulceration is to interfere with gastric physiology as much as possible!) It is clear from our observations that physiological conditions are far from normal after Billroth I resections. No distal sphincter action is developed, and the gastric contents are consequently no longer retained and subjected to the combined effects of repeated gastric peristalsis and admixture with gastric juice but are hurried through the stomach into the alkaline medium of the duodenum with such rapidity as to abolish gastric digestive function entirely.

The restriction of the size of stoma practised in the Hofmeister-Finsterer type of Polya resection, and much vaunted by Shanks (1934), Ogilvie (1935), and Lake (1948) as a means of controlling the efflux of gastric contents, has in our experience been almost equally disappointing. We find with Bruusgaard (1946), Porter and Claman (1949), and O'Neill (1950) that the emptying of the gastric stump is almost always as rapid in these cases as after the Polya operation with wide stoma. Even with a specially large valve and small stoma recommended by Porter and Claman (1949), we have not succeeded in achieving gastric retention of the barium meal.

Filling of Small Gut

After Billroth I resections the emptying of the stomach contents directly into the duodenum often causes dilatation of the most dependent part of the duodenal loop, presumably because this assumes the reservoir

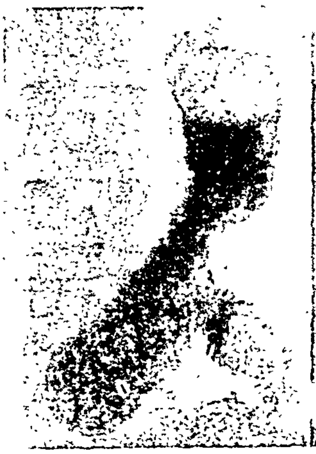


Fig. 2.

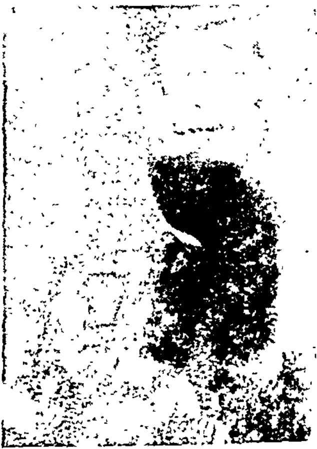


Fig. 3.

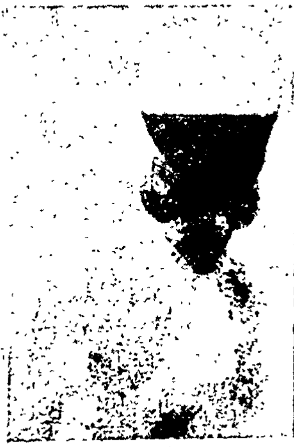


Fig. 4.

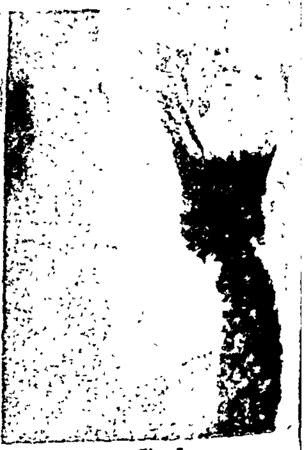


Fig. 5.

Fig. 2—Radiograph immediately after barium meal in patient treated by Billroth I subtotal gastrectomy, showing small size of gastric remnant, second and third parts of duodenum drawn up to left, and dilatation of third part of duodenum.

Fig. 3—Radiograph immediately after barium meal in patient treated by Polya-Moynihan gastrectomy, showing *retrograde* filling of afferent jejunal limb and duodenum, and bulging of jejunum opposite stoma.

Fig. 4—Radiograph after barium meal in patient treated by Hofmeister-Finsterer gastrectomy: *barium has entered afferent jejunal limb as well as efferent*, and has outlined duodenal stump.

Fig. 5—Radiograph immediately after barium meal in patient treated by Hofmeister-Finsterer gastrectomy, showing complete absence of reflux into afferent jejunal limb.

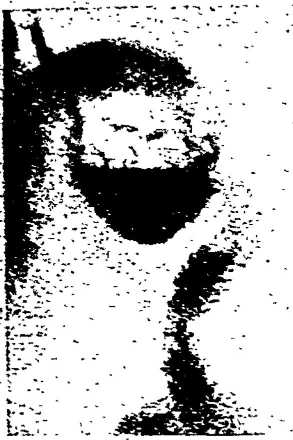


Fig. 6.

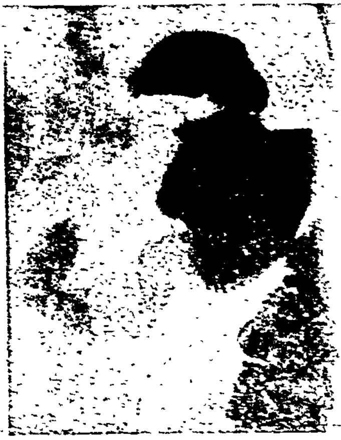


Fig. 7.

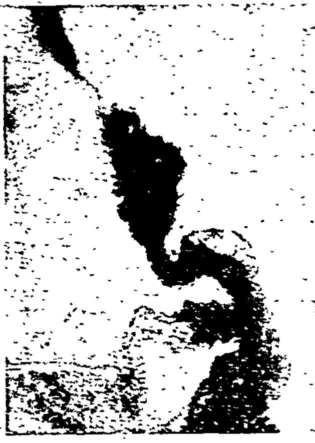


Fig. 8.

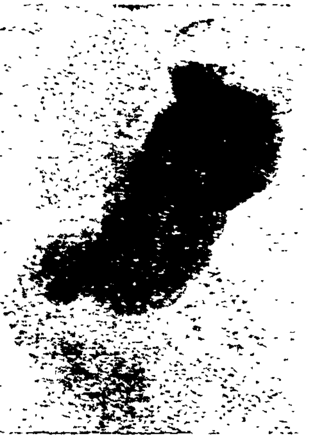


Fig. 10.

Fig. 6—Radiograph after Hofmeister-Finsterer gastrectomy, showing reflux of barium as far as top of valve on lesser curve, and bulging of jejunum opposite stoma.

Fig. 7—Radiograph after total gastrectomy with end-to-side œsophagojejunostomy and entero-anastomosis, showing gross proximal jejunal dilatation.

Fig. 8—Radiograph after total gastrectomy and œsophagojejunostomy by Roux's method, showing filling of side limb of jejunum and duodenal stump.

Fig. 10—Radiograph after partial gastrectomy with colon replacement, showing immediate filling deceptively resembling normal appearance of stomach.

function of the stomach. In some cases dilatation of the upper jejunum was also noted.

After the Pólya-Moynihan type of gastrectomy with gastrojejunal anastomosis the wide stoma usually allows food to enter both afferent and efferent limbs of the jejunal loop. Indeed, because the afferent or proximal limb runs to the greater curve or under part of the stomach (fig. 1b), gastric contents often gravitate primarily into it. Radiologically the proximal jejunal limb and the duodenum as far as the stump were outlined by the opaque meal in 60% of the Polya gastrectomy cases investigated.

After the Hofmeister-Finsterer operation the closed upper three-quarters of the gastric cross-section and intact jejunal wall sutured to this portion should in theory act as a valve, deflecting gastric contents from entering the afferent jejunal limb, which here runs to the lesser curve (fig. 1c). Our postoperative radiological investigations show that in a few cases after the operation food does pass into the proximal limb as far as the top of the valve, and occasionally reflux occurs into the duodenal stump, but in most of the cases filling of the proximal limb is entirely obviated. The claims of Finsterer and Cunha (1931), Ogilvie (1935), Maingot (1948), and Mimpriss and Birt (1948) regarding the efficacy of this valve are thus in the main confirmed.

After total gastrectomy with end-to-side œsophagojejunostomy and jejunojejunostomy (fig. 1e) a barium meal showed immediate filling of both limbs of the jejunal loop and of the duodenal stump. The *Roux method* of establishing the œsophagojejunostomy (fig. 1f) sometimes avoided reflux into the duodenal stump.

Clinical Observations

In assessing the frequency of dumping in gastrectomised patients an essential preliminary was to define exactly what one meant by this term, which has been used by different workers to mean different things. Thus many Americans, such as Eusterman (1947), refer to dumping as an essentially vasomotor phenomenon with weakness, generalised warmth and sweating, palpitations, nausea, borborygmi, and even diarrhœa, and hardly mention the sensation of epigastric fullness. Capper and Butler (1951), though emphasising abdominal discomfort as a component of dumping, claim that this is usually situated at a higher level in the epigastrium than is the sense of fullness regularly experienced by most patients after high gastrectomy, and that it is always accompanied by constitutional and vasomotor symptoms as well. According to them a sense of epigastric fullness and nausea alone do not constitute dumping.

We have not found it possible to draw such a sharp line of distinction, and regard the attempt to do so as highly artificial. In our experience there is a simple gradation between the mild postcibal epigastric fullness experienced by most of our patients after gastrectomy and the severe abdominal discomfort, sometimes accompanied by nausea, regurgitation of bile, or vomiting, found in the patients with undoubted dumping. Not all the latter patients have had vasomotor symptoms such as faintness, flushing, or sweating. It is the epigastric fullness and inability to eat substantial meals that constitute the gastrectomised patient's main grievance in the early weeks after operation, and even later in the more severe cases.

In assessing the severity of dumping in our cases, we have therefore concentrated mainly on the amount of postcibal epigastric discomfort, though we have paid some attention to other symptoms as well. We have found that the largest meal that the patient can eat without discomfort is a helpful guide in this respect. Slight epigastric fullness after a meal exceeding three-quarters of the size normally eaten before operation, and seldom accompanied by other symptoms, we have rated as mild dumping. Fullness brought on by a meal greater than half the patient's preoperative normal, and associated sometimes with nausea but rarely with faintness or sweating, we have classed as moderate dumping. The term severe dumping we have reserved for those patients who cannot take more than very small meals without considerable epigastric fullness, nausea, and often regurgitation of bile, vomiting and faintness, flushing of the head and face, or profuse sweating.

In this inquiry we have not considered other post-gastrectomy syndromes, and in particular have not included examples of the hypoglycæmic late dumping phenomenon. We recognise that the first two grades of dumping, as defined by us, occasion the patients relatively little inconvenience, and can be largely obviated by slight adjustments of diet compatible with a normal existence. By many surgeons they might not be included at all, and only the cases in the third group with serious discomfort considered as exhibiting the dumping syndrome.

The incidence of mild, moderate, and severe dumping in our gastrectomy cases as estimated six months after operation is shown in the accompanying table.

Discussion

HEIGHT OF GASTRECTOMY AND INCIDENCE OF DUMPING

It is commonly held by surgeons that dumping is more frequent and severe after a really high subtotal gastrectomy than a relatively low one. In our series, therefore, it is interesting to compare the results in cases treated by subtotal gastrectomy with Polya-Moynihan anastomosis and in those submitted to low partial gastrectomy with a similar type of anastomosis. In these two groups an exactly similar technique was used except for the difference in the height of the gastric resection. The table shows that there is a slight difference in the incidence of dumping in these two groups, but in these relatively short series of cases it is not statistically significant, and it would need to be maintained in very much longer series to carry weight. Actually the difference in the height of the two forms of gastrectomy was not very great but was, in our opinion, the greatest possible within the range of therapeutically valuable resections. An instructive comparison would have been between cases treated by subtotal gastrectomy and those treated by gastro-enterostomy, but the latter operation has rarely been used by us, and insufficient cases submitted to it were available.

INCIDENCE OF DUMPING SIX MONTHS AFTER DIFFERENT TYPES OF GASTRECTOMY

Type of Gastrectomy	No. of cases	No. of patients experiencing dumping			
		Mild	Moderate	Severe	Total
Total	14	4	5	5	14 (*100%*)
Subtotal ($^3/_4$–$^4/_5$):					
With Billroth I anastomosis	45	9	19	5	33 (*73·3%*)
With Polya-Moynihan anastomosis ..	60	20	19	6	45 (*75%*)
With Hofmeister-Finsterer anastomosis..	53	17	16	7	40 (*75·5%*)
Low partial ($^1/_2$–$^2/_3$):					
With Polya-Moynihan anastomosis ..	52	13	18	5	36 (*69·2%*)
Total	224	63	77	28	168 (*75%*)

The number of patients examined after total gastrectomy is small; but, so far as our inquiry goes, it points to a higher incidence and greater severity of dumping after this operation than after any form of partial gastrectomy, and it is certainly our clinical impression that these patients had much more trouble with dumping in the early stages after operation than did subtotal-gastrectomy patients. Their frequent inability to take more than very small meals was one of the problems in the management of these patients in the convalescent period, but we have been agreeably surprised by the manner in which their capacity for food has gradually increased, with the result that after six months or so several of them are taking a substantially normal diet with only slight restrictions.

INCIDENCE OF DUMPING RELATIVE TO TYPE OF ANASTOMOSIS

Most of the cases in this series were treated by subtotal resection, completed according to the Billroth I, Polya-Moynihan, or Hofmeister-Finsterer technique. In these cases the height of gastrectomy was kept about constant, the only variable factor being the method of final anastomosis; hence it is possible to compare the relative merits of these three techniques in avoiding the dumping syndrome. The table shows that the incidence of dumping was roughly the same after all three operations, the slight differences noted not being statistically significant. As regards the Billroth I operation, our findings conflict sharply with those of Mimpriss and Birt (1948) and O'Neill (1950), who obtained a much lower incidence of dumping after this operation than after resections of the Polya type, and are even more at variance with the observations of Capper and Butler (1951), who claim that dumping never occurs after the Billroth I operation. We think that this discrepancy may be partly explained by the fact that in the performance of a Billroth I gastrectomy many surgeons, feeling that a really high resection is not essential in the treatment of gastric ulcer—the usual lesion submitted to this operation—and being not unnaturally concerned about the prospects of bringing the stomach stump and duodenum together subsequently without tension, remove less stomach in this operation than they do in a Polya gastrectomy. The account of the operative technique and the postoperative radiographs published by Morley and Roberts (1928) indicate clearly that the Billroth I gastrectomy in the past has often been a very limited resection indeed, involving removal of little more than the pyloric antrum and a strip of stomach along the lesser curve. *In our cases treated by subtotal* gastrectomy we have been careful to keep the height of the resection constant throughout; and, if gastroduodenal approximation was difficult after resection of this extent, the effort to carry out a Billroth I operation was abandoned in favour of a gastrojejunal anastomosis; hence any possible error due to variations in the extent of the resection has been eliminated.

As regards the relative merits of the left→right Polya-Moynihan type of gastrojejunal anastomosis with full-length stoma and the right→left Hofmeister-Finsterer anastomosis with valve on the lesser curve, we cannot support the claims of Ogilvie (1935), Maingot (1948), Lake (1948), and others that the latter operation confers a high degree of immunity to dumping symptoms. The table shows that the incidence of mild, moderate, and severe dumping was roughly the same after these two operations. Further, the 12 patients treated by the modification of the Hofmeister-Finsterer technique recommended by Porter and Claman (1949), with specially large valve and very small stoma, did not seem to fare *any better symptomatically than those treated by* more orthodox modifications of the Polya operation.

MECHANISM OF PRODUCTION OF DUMPING SYNDROME

In the light of the foregoing clinical and radiological *findings certain criticisms of the* theories advanced to explain the production of the dumping syndrome seem to be justified. The contention of Capper and Butler (1951) that dumping after partial gastrectomy is due to stretching of the gastric stump seems to be invalidated by our observation that dumping is at least as common, and probably commoner, after total gastrectomy. The fact that the patients who have no gastric stump and whose *œsophagus opens directly into the* small intestine often suffer severely from dumping suggests that distension of the small gut is responsible for the dumping. As we have seen, after all forms of partial gastrectomy the stomach remnant, deprived of its sphincter, loses its power of active retention of food and becomes entirely passive, transmitting the meal usually immediately to the small intestine. Hence it is reasonable to suppose that *sudden distension of the small intestine* may also be the mechanism responsible for dumping symptoms after partial gastrectomy. In 5 of our post-gastrectomy cases distension of the balloon of a Miller-Abbott tube, sited under radiological control in the efferent jejunal limb, has reproduced the sensation of epigastric fullness experienced by these patients when affected by the dumping syndrome.

From our finding that dumping occurs with roughly e same frequency and severity in cases treated by fferent techniques of gastro-intestinal anastomosis ter gastric resection, we must conclude that sudden stension of any part of the upper intestinal tract may oduce dumping. After Billroth I gastrectomies it is esumably the stretching of the duodenum that is sponsible, though, owing to the rapid transit of the eal to the jejunum, jejunal distension may also be a ctor. After Polya-type gastrectomies with gastro-junostomy, jejunal distension is the mechanism, the nly point in dispute being whether distension of the roximal or afferent limb of the jejunal loop as far as e duodenal stump is specially significant, or whether istension of the distal or efferent limb is equally nportant. The fact that the incidence of dumping was bout the same in cases treated by the Hofmeister-insterer gastrectomy, in which our radiological investiations show that filling of the proximal loop was usually voided; as it was in those having the Polya-Moynihan astrectomy, after which filling of the afferent limb and uodenum was usually present, indicates that filling of the roximal limb per se cannot be regarded as ætiologically pecially significant. We know further that in many of ur cases with severe dumping the afferent limb was not illed, and many patients who had no dumping at all, r only the mildest symptoms, had a gross reflux of food nto the afferent limb and duodenum.

Our data do not enable us to discuss whether the symptoms are due to distension of the bowel or, as Welbourn (1951) suggests, to the hyperperistalsis that develops in response to this distension. Whatever the precise mechanism, the bowel in time clearly acquires a tolerance to the distension in most cases. Radiologically this was suggested by the finding in many cases of permanent dilatation of the duodenum or of the upper jejunum, and clinically it is reflected in the gradual diminution in the severity of the symptoms. This can best be exemplified by citing the findings on reassessing our cases symptomatically eighteen months after operation; 141 subtotal and partial gastrectomies had been performed sufficiently long ago for this to be done. The number of patients who still had dumping symptoms was 67 (47·5%), but the symptoms were severe in only 10 (7·1%), and of these only 3 were sufficiently disabled by dumping to doubt whether the operation had been worth while. As a drawback to gastrectomy dumping should not be overrated.

SUMMARY

The incidence and mechanism of dumping syndrome has been studied in 224 patients six months after various forms of partial and total gastrectomy.

In the clinical assessment of the severity of dumping, importance was attached chiefly to postprandial epigastric fullness and to limitation in the size of meals enforced on patients by this sensation.

Six months after operation 168 (75%) of the patients had dumping, which was severe in 28 (12·5%). Spontaneous amelioration occurred in time, and reassessment of 141 patients eighteen months after subtotal or partial gastrectomy showed that though 67 (47·5%) still had dumping, this was severe in only 10 (7·1%).

The incidence of dumping was not related to the type of partial gastrectomy, but was slightly higher the more extensive the resection. In total gastrectomy (14 cases) dumping seemed much more frequent and severe than after subtotal or partial gastrectomy.

Radiography showed that after all forms of partial and subtotal gastrectomy the gastric remnant loses its power of active retention of food, which under the influence of gravity passes immediately into the small intestine. The weight of the meal is thus borne by the small intestine, and chronic dilatation of the duodenum or of the upper jejunum was not infrequently demonstrated radiologically. It is considered that this duodenal or jejunal distension is the factor responsible for dumping symptoms.

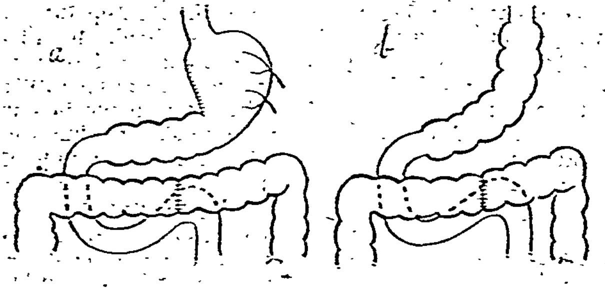


Fig. 9—Colon replacement of stomach after: *a*, partial gastrectomy; *b*, total gastrectomy. Implant of transverse colon arranged antiperistaltically in both instances.

Reflux of food into the afferent jejunal loop and duodenum is not regarded as specially important in the ætiology of dumping, because after the Hofmeister-Finsterer type of gastrectomy such reflux is often avoided, yet the dumping syndrome is no less frequent after this operation than after the Polya-Moynihan gastrectomy, which is nearly always followed by reflux. Similarly, stretching of the gastric stump cannot be an important factor because dumping often occurs after total gastrectomy.

Colon Replacement

Since this paper was completed, the work of Moroney (1951) on the use of a transplant of an isolated segment of transverse colon to provide a gastric reservoir after partial gastrectomy, and of Lee (1951) on the use of transposed terminal ileum, cæcum, and ascending colon for the same purpose after total gastrectomy, has stimulated us to incorporate this idea in some of our more recent operations. We have now done 12 subtotal gastrectomies with implantation of a 6-in. length of transverse colon between the gastric remnant and the duodenum (fig. 9*a*), and 3 total gastrectomies with interposition of a similar but rather longer segment of transverse colon between the lower end of the œsophagus and the duodenum (fig. 9*b*). In all the cases the colon graft was placed antiperistaltically—i.e., with the splenic-flexure end to the œsophagus or the stomach, and the hepatic-flexure end to the duodenum. In 1 total gastrectomy and 1 subtotal gastrectomy the coloduodenal anastomosis leaked; in the former case the patient died. The other patients all recovered without untoward incident.

We were sceptical about the likelihood that these colon implants would act satisfactorily as a reservoir, because the patients are still without a sphincter apparatus to prevent the food from passing immediately through the colon into the duodenum. But it was hoped that the antiperistaltic arrangement of the colon segment might have some effect in delaying the transit of gastric contents to the small intestine. We note that Moroney (1951) and Lee (1951) claim that there is both retention of food in the gastric stump and colon reservoir for several hours, and considerable reduction in the incidence and severity of dumping symptoms.

Our experience has not been so encouraging. Radiologically there has been delay up to one and a half to two hours in the emptying of the stomach remnant and colon transplant (fig. 10) in 4 cases, but in the remaining patients treated by this method, including the 2 surviving total-gastrectomy patients, emptying was rapid, as in more orthodox gastric resections. Clinically, 1 patient who had rapid emptying could eat full-sized meals with no discomfort of any kind from the beginning of convalescence, but most of the others are pursuing much the course of the average gastrectomy case, and have had to eat small meals during the first few weeks after operation. One patient has severe discomfort after food, and this is only slowly improving. These assessments, however, are being made within two or three months of operation and are not quite comparable with those made in our other cases. At this stage our impression is that the method of colon replacement neither eliminates dumping nor sufficiently minimises it to warrant the added intricacy and increased danger of this procedure.

We wish to thank Dr. E. Rohan Williams, director of the department of diagnostic radiology, St. Mary's Hospital, for permission to undertake the radiological examinations in his department, and the radiographers for their technical assistance.

REFERENCES

Barnes, C. G. (1947) *Lancet*, ii, 536.
Brunsgaard, C. (1946) *Acta chir. scand.* 94, 1.
Butler, T. J., Capper, W. M. (1951) *Brit. med. J.* i, 1177.
Capper, W. M., Butler, T. J. (1951) *Ibid*, ii, 265.
Finsterer, H., Cunha, F. (1931) *Surg. Gynec. Obstet.* 52, 1099.
Eusterman, G. B. (1947) *Gastroenterology*, 8, 575.
Gilbert, J. A. L., Dunlop, D. M. (1947) *Brit. med. J.* ii, 330.
Hurst (Hertz), A. F. (1913) *Ann. Surg.* 58, 466.
Irvine, W. T. (1948) *Brit. med. J.* ii, 514.
Kennedy, C. S., Reynolds, R. P., Cantor, M. O. (1947) *Surgery*, 22, 41.
Lake, N. C. (1948) *Brit. med. J.* i, 285.
Lee, C. M. jun. (1951) *Surg. Gynec. Obstet.* 92, 456.
Machella, T. E. (1949) *Ann. Surg.* 130, 145.
— (1950) *Gastroenterology*, 14, 237.
Maingot, R. (1945) *Postgrad. med. J.* 21, 211.
— (1948) Abdominal Operations. 2nd ed., London; p. 229.
Mimpriss, T. W., Birt, St. J. M. C. (1948) *Brit. med. J.* ii, 1095.
Mix, C. L. (1922) *Surg. Clin. N. Amer.* 2, 617.
Morley, J., Roberts, W. M. (1928) *Brit. J. Surg.* 16, 239.
Moroney, J. (1951) *Lancet*, i, 993.
Muir, A. (1949) *Brit. J. Surg.* 37, 165.
Ogilvie, W. H. (1935) *Brit. med. J.* i, 457.
O'Neill, T. (1950) *Ibid*, ii, 15, 528.
Porter, H. W., Claman, Z. B. (1949) *Ann. Surg.* 129, 417.
Shanks, S. C. (1934) *Brit. med. J.* ii, 1032.
Welbourn, R. B. (1951) *Proc. R. Soc. Med.* 44, 773.

THE ROUTINE TESTING OF THE SENSITIVITY OF BACTERIA TO ANTIBIOTICS

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IN consequence of the increased use of antibiotics in clinical medicine, a large proportion of the work of a routine bacteriological laboratory must now be devoted to tests of the sensitivity of bacteria to these substances. In view of the number of antibiotics to be investigated it has become essential to use as simple a method as possible; but this must not involve any sacrifice of reliability, in which respect, in our opinion, the widely used filter-paper-disc method is at a disadvantage. Since this method, like many others, depends on the diffusion of the antibiotics into the medium, the size of the zones of inhibition must be governed to some extent by such factors as the composition and depth of the medium and the amount of surface moisture. The size of the bacterial inoculum is also of importance in determining the apparent degree of sensitivity to some antibiotics. Though it is possible to control each of these factors and thus to standardise the method, in a routine laboratory it is often inconvenient to apply the required amount of control.

In the method described below, diffusion of the antibiotics does not take place, and many of the shortcomings of the filter-paper-disc method are thus eliminated. Further, the medium on which the tests are made has the property that, within very wide limits, the size of the bacterial inoculum has no bearing on the apparent sensitivity. A third advantage inherent in this method is that the organisms are tested against known concentrations of the antibiotics, so that a semi-quantitative estimate of the degree of sensitivity is obtained. This gives the clinician a better opportunity to assess the likely response of his patient to a given antibiotic, having regard to the site of the infection and the probable concentration of the antibiotic that can be attained in it.

PRINCIPLE

The method is an extension of a technique that has been in use for some years in this laboratory for determining the sensitivity of organisms to sulphonamides. In this test, which is similar to that advocated by Harper and Cawston (1945), the organism is inoculated on to two culture plates, in one of which is incorporated a known concentration (8 mg. per 100 ml.) of the sulphonamide, while the other serves as a control. After incubation the sensitivity or resistance of the organism is assessed by comparing the growth on the sulphonamide-containing plate with that on the control. For this technique to be satisfactory the size of the bacterial inoculum must not influence the growth on the sulphonamide plate, and, in the light of the work of Harper and Cawston, it was found that on Levinthal's medium (Levinthal 1918) this inoculum effect was reduced to negligible proportions. This medium also has the advantage that it will support the growth of all the organisms commonly encountered in a routine laboratory (except *Mycobacterium tuberculosis*).

INVESTIGATION OF LEVINTHAL'S MEDIUM

For the method to be applicable to antibiotics, the influence of inoculum size must be negligible for each antibiotic used, and the potency of the antibiotics in the medium must be retained for a considerable time, since it is likely to be impracticable to prepare the plates at very short intervals. Levinthal's medium satisfies these conditions. Within very wide limits the size of the inoculum has no influence on the apparent sensitivity to penicillin, streptomycin, chloramphenicol, terramycin, and aureomycin; and, with the possible exception of aureomycin, the potency of each of these antibiotics in Levinthal's medium shows no detectable diminution after storage for two weeks at 4°C.

The effect of inoculum size and the keeping properties of the antibiotics were investigated simultaneously for each antibiotic. The technique was as follows:

(1) A suitable test organism of known sensitivity was selected.

(2) Twofold serial dilutions of the antibiotic under test were made in molten Levinthal's medium cooled to about 60°C, and three plates were poured from each dilution. The concentrations were selected in such a way that the end-point of the titration with the known test organism would fall near the highest dilution. For example, with penicillin the Oxford H staphylococcus (sensitive to $^1/_{50}$ unit per ml.) was the test organism, and the concentrations of penicillin in the plates were $^1/_2$, $^1/_4$, $^1/_8$, $^1/_{16}$, $^1/_{32}$, and $^1/_{64}$ unit per ml. Three control plates of plain Levinthal's medium were also poured.

(3) Serial dilutions of a twenty-four-hour broth culture of the test organism were made by passing a loopful of the culture successively through 9 separate drops of physiological saline solution on a paraffin-coated slide (about a fivefold to tenfold dilution at each stage).

(4) One set of the plates, including a control, was dried in the incubator for thirty minutes, after which each dilution of the culture (including the undiluted culture) was streaked across each of these plates. In this way ten titrations were set up on the plates with the inoculum size varying from undiluted broth culture to about a millionfold dilution of this culture. Thus it was possible, after overnight incubation at 37°C, to determine the degree to which inoculum size influenced the end-point of the titration.

(5) The remaining two sets of plates were stored at 4°C, and procedures 3 and 4 were repeated on each set in turn four and eight days respectively after they had been prepared. By comparison of the end-points on these plates with that on the first set any loss of potency of the antibiotic could be assessed.

With penicillin, streptomycin, chloramphenicol, and terramycin the results were uniformly constant. No change in the end-point was detectable after eight days' storage of the plates, and in subsequent experiments it was found that this limit could well be extended to fourteen days. As regards the inoculum size, it was found in each case that a very slight lowering of the end-point—i.e., an apparent increase in resistance of the organism—occurred when the inoculum was made from the undiluted culture. With this inoculum a trace of growth appeared on the plates containing the highest dilution of the antibiotic to cause complete inhibition of all other inocula, but this effect was regarded as so slight that it could be ignored in practical tests. It is interesting that no greater inoculum effect was observed with streptomycin than with the other antibiotics, for in many other media the size of the inoculum makes a considerable difference to the apparent sensitivity of organisms to this substance (May et al. 1947).

With aureomycin the influence of inoculum size was no greater than it was with the other antibiotics mentioned above. As regards the keeping properties of aureomycin in Levinthal's medium, it was found that the potency had diminished to half the original strength after eight days' storage. This diminution was much less than had been expected, and it is questionable whether it is sufficient to condemn the use of this method in routine practice, where highly accurate estimations are not required. Aureomycin plates should not, however, be used more than eight days after their preparation.

OTHER MEDIA INVESTIGATED

Levinthal's medium was used in the preliminary investigations because it was known to give satisfactory results with the sulphonamides. It also has the advantage over many media that *Hæmophilus influenzæ* grows well on it. There are, however, certain practical difficulties in its preparation in bulk, and two alternative media were therefore investigated. These were Fildes's peptic blood digest medium and unfiltered boiled blood-agar. Both of these media had the disadvantage that occasional organisms appeared to be resistant to sulphonamides incorporated in them, even though quite sensitive to the same sulphonamide in Levinthal's medium—i.e., the inoculum effect was not overcome for sulphonamides. After trials of several variations of these media it was concluded that a modification of Levinthal was the most generally satisfactory.

CONCENTRATIONS OF ANTIBIOTICS USED

Since the organisms being tested are exposed to known concentrations of each antibiotic, it is logical to select concentrations which bear a definite relation to those which can easily be attained in the human body. It was decided to test each organism against two strengths of each antibiotic: (1) equivalent to the expected blood level about four hours after a routine dose of the antibiotic; and (2) equivalent to the level that can be attained in the urinary tract after a routine dose, or by local application of the antibiotic to the infected area.

Clearly no fixed rules can be applied in determining these levels, owing to individual variations, but it was with these considerations in mind that the following test concentrations were selected:

	Penicillin	*Strepto-mycin*	*Chloram-phenicol*	*Terra-mycin*
Blood ..	0·25 u/ml.	5 µg./ml.	10 µg./ml.	5 µg./ml.
Urine ..	5 ,,	25 ,,	50 ,,	50 ,,

Tests with aureomycin have not yet been brought into routine use, but probably satisfactory concentrations would be the same as those for terramycin.

In the test as used in this laboratory a sulphonamide (sulphadimidine) is also included in the series. One concentration only (8 mg. per 100 ml.) is used for this substance.

PREPARATION OF MEDIUM

Levinthal's medium is a filtrate of heated horse blood added to agar. It is prepared as follows:

20% defibrinated horse blood in nutrient broth is heated in a water-bath at 80°C until all the blood has been converted into "chocolate" (the time required varies with the bulk, but usually about an hour's heating suffices for 2 litres of blood broth). The precipitate is removed by filtration, first through muslin, and next paper pulp, and finally the filtrate is cleared and sterilised by Seitz filtration. The final pH should be between 7·6 and 7·8. The filtrate is stored in 95 ml. quantities. The agar to which this filtrate is later added is a nutrient broth containing 4% shred agar *w/v* (filtered). It is stored in 100 ml. quantities.

The antibiotic solutions are prepared in such concentrations that 5 ml. of each, when added to 195 ml. of Levinthal agar, produces the appropriate concentration for use. These solutions, which should be prepared on the day the plates are made, are as follows:

	Penicillin	*Strepto-mycin*	*Chloram-phenicol*	*Terra-mycin*
Weak ..	10 u/ml.	200 µg./ml.	400 µg./ml.	200 µg./ml.
Strong ..	200 ,,	1000 ,,	2000 ,,	2000 ,,

The sulphadimidine solution (320 mg. per 100 ml.) may be prepared in bulk, for it keeps indefinitely.

For preparation of the plates ten bottles of 4% agar are melted and cooled to 60°C. To each is added 95 ml. of Levinthal filtrate after previous warming to 60°C. 5 ml. of the appropriate antibiotic or sulphonamide solution is added to each bottle and, after careful mixing, eight plates and eight slopes in bijou bottles (see below) are poured from each. Eight are required so that one set may be available each day of the week, with one set in reserve. Eight controls containing no antibiotic are also poured. All the plates and slopes are stored at 4°C.

TECHNIQUE AND RESULTS OF TEST

(1) All the specimens for bacteriological examination are inoculated on to the routine media of choice. After incubation significant organisms are subcultured into nutrient broth (serum broth is used for streptococci and pneumococci) and incubated at 37°C for four or five hours. Each culture is numbered.

(2) A set of antibiotic plates (one of each concentration of all the antibiotics, one sulphonamide, and one control) is dried in the incubator for thirty minutes.

(3) The broth culture of each organism is subcultured on to each of the plates. Since the size of the inoculum is of no importance, the implant can be small, and it is possible to test at least 20 organisms simultaneously on one set of plates. For convenience in identification each implant may be made in the shape of the number of the parent culture. Proteus strains are inoculated on to the slopes in bijou bottles to avoid overgrowth of other organisms on the plates.

(4) The plates are incubated overnight at 37°C, after which the sensitivity of each organism to the two strengths of each antibiotic is assessed by comparison of the growth on the test plates with that on the control. It has been our custom to report the sensitivity of organisms in terms of the lowest concentration of the antibiotics causing complete inhibition of growth. Where partial growth occurs on a plate we have assumed, for clinical purposes, that the organism is resistant to that concentration. A typical report is shown below:

Organism: Staph. aureus
Sensitivity to:

Sulphadimidine	Nil
Penicillin	0·25 u/ml.
Streptomycin	25 µg./ml.
Chloramphenicol	10 µg./ml.
Terramycin	5 µg./ml

Organism	No. tested	*Percentage of organisms sensitive to: Penicillin (u/ml.) 0·25	Penicillin (u/ml.) 5	Streptomycin (µg./ml.) 5	Streptomycin (µg./ml.) 25	Chloramphenicol (µg./ml.) 10	Chloramphenicol (µg./ml.) 50	Terramycin (µg./ml.) 5	Terramycin (µg./ml.) 50	Sulphadimidine 8 mg./100 ml.
Staph. aureus	338	42	66	65	78	90	97	99	99	49
Strep. pyogenes	57	98	100	19	88	100	100	100	100	33
Strep. viridans	54	70	98	18	93	100	100	98	100	56
Pneumococcus	36	100	100	25	92	100	100	100	100	78
Enterococcus	75	5	79	0	28	96	100	89	89	0
Coliform bacilli	262	0	0·7	29	73	78	92	80	90	58
Ps. pyocyanea	133	0	0	0	6	0	2	0	72	0
Proteus	103	0	10	4	47	24	79	6	10	20
Sh. sonnei	30	0	0	53	97	100	100	83	100	100

* Only organisms completely inhibited by the antibiotics are included. Those showing partial inhibition have been counted as resistant.

The accompanying table gives the findings for some of the common bacteria tested over a period of eleven months.

SUMMARY

A method for the routine testing of the sensitivity of bacteria to antibiotics is described.

The concentrations of the antibiotics against which the organisms are tested are designed to indicate the likely response of the patient to each substance in systemic, urinary, or "local" infections.

The findings for several common organisms during eleven months' use of the test are given.

We wish to thank Sir Alexander Fleming for his helpful advice and criticism.

REFERENCES

Harper, G. J., Cawston, W. C. (1945) *J. Path. Bact.* 57, 59.
Levinthal, W. (1918) *Z. Hyg. InfectKr.* 86, 1.
May, J. R., Voureka, A. E., Fleming, A. (1947) *Brit. med. J.* i, 627.

TREATMENT OF PARKINSONISM IN A CHILD

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IN his report on the effects of encephalitis lethargica Parsons (1928) described the family tragedies of the epidemic which followed the first world war. The wage-earner or the mother was the victim in some homes, but in others children or young adults were infected. "In children," he wrote, "the results are peculiar and deplorable . . . most pathetic of all is the dribbling 'old man' of fifteen years or so who sits hunched up in his chair, stiff and impassive, slowly dying of parkinsonism."

In a disease where specific cure is unknown many forms of treatment have naturally been tried, but few are of value even for the relief of symptoms. The Matheson Commission (1939) discussed over fifty methods of treatment; they reported that the only exceptions to the general therapeutic failure—atropine, hyoscine, and stramonium—required doses which produce unpleasant side-effects. These drugs reduce the muscular rigidity, the tremor, and the drooling of excessive salivation. Later the anti-histamine drugs were found to be beneficial in some cases of parkinsonism, and since 1948 reports have appeared on new antispasmodics such as 'Artane' (benzhexol hydrochloride) and 'Lysivane' (ethopropazine hydrochloride), which relax smooth muscle and inhibit the parasympathetic nervous system.

Parkinsonism in a child is now comparatively rare it was considered worth while recording this case tre with artane.

CASE-HISTORY

A boy, aged 11, was the fourth child in a family of born to healthy, unrelated parents. His physical and m development were normal and he was a bright, active, adventurous child with a keen sense of humour.

In early September, 1950—at a time when poliomy was about—he went swimming in an indoor pool, an arriving home he was seen to be pale and exhausted. He most unlike himself; and on the third day of this unna lethargy he was pushed by another boy and bruised his on the pavement. The odd tiredness persisted and developed an intermittent tremor of the hands, arms, legs. Even on direct questioning he denied any headache, or disturbance of sleep.

He was admitted to hospital on Sept. 26. His face expressionless and he held his arms flexed and str adducted as he walked. A coarse involuntary tremor of arms was present, the pupils reacted sluggishly to light, the tendon and abdominal reflexes were difficult to e Muscle tone was not appreciably altered at this stage, though he could draw quite cleverly he seemed dull and of response. Lumbar puncture and all other investiga proved negative. Despite a normal cerberospinal fluid most likely diagnosis was thought to be postenceph parkinsonism.

Though no reference can be found to the value of aureom or chloramphenicol in encephalitis lethargica, these were given in the hope of some benefit, but it was impos to say if they had any effect or not.

When he was discharged on Oct. 11 he was walking clu with an early parkinsonian stoop.

He was seen again two weeks later when his mother tho he had been more cheerful and active, but to the exan there was little obvious change.

If there had been improvement it was short-lived, fo had to be readmitted on Jan. 25, 1951. He was always t and had gained over 10 lb. in weight. He was inattenti school where the standard of his work had suddenly fa Everybody who saw him said how unwell he looked. His was mask-like and his mouth open, as is common in such (Ford 1944). The gait was stiff and much more obvi parkinsonian with the left side worse than the right. slumped awkwardly in a chair with some neck retrac Every effort produced short expiratory grunts and saliva from his mouth when he leaned forward. Cogwheel spasti was present in the arms and the reflexes were still diminis The sensory nervous system was intact, but his speech slow, monotonous, and indistinct. Despite the tardines his replies, psychometric testing fixed his intelligence quot at 135. The diagnosis was now in no doubt. He conti to deteriorate and in March it was decided to carry o *clinical trial with artane.*

TREATMENT

During a programme of thirteen weeks the pat received amphetamine, 'Benadryl,' artane, and i control tablets, either singly or in suitable combina The order in which the drugs were given was left to discretion of the hospital pharmacist and was unkn to the physician. The only restriction made was tha period of trial with artane should be preceded followed by two weeks on similar but inert tablets.

Benadryl was given in doses of 25 mg. twice daily increased to a maintenance dose of 50 mg. three t daily by the fourth day. Doses of 5 mg. of amphetar were given at breakfast and lunch. Artane began a dose of 0·5 mg. once daily and was steadily incre to 7 mg. daily by the seventh day. When control ta were given the dosage was increased in the s way.

The boy and his mother knew nothing about the na of the tablets nor was the physician told until the of the experiment during which weeks the various d had been given.

The patient was seen each week. His mother interviewed apart and gave her account of his condi during the preceding week. The boy was then obser

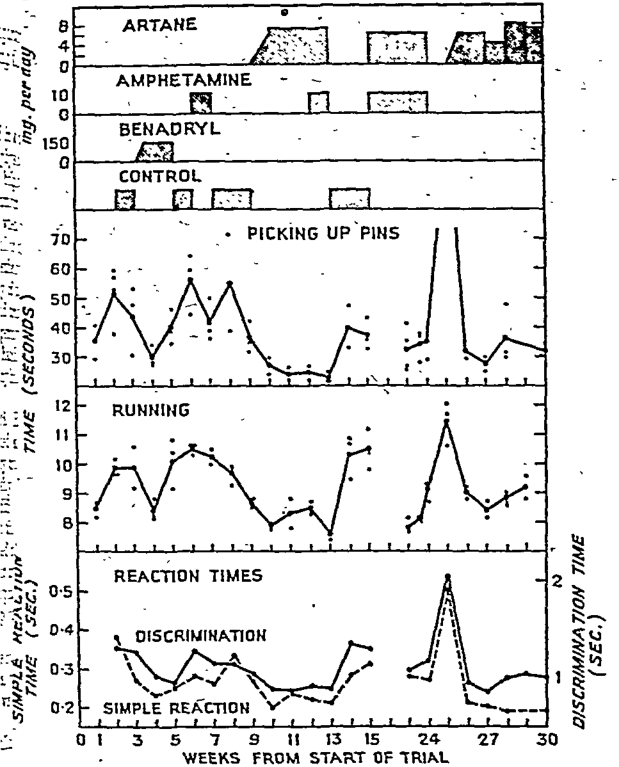

Fig. 1—Effects of artane, amphetamine, benadryl, and control tablets on coördination tests and reaction times.

walking and undressing before he was examined. Several simple tests were designed to time his response to a stimulus, and to assess the tonicity of his muscles and the degree of tremor. Six pins had to be picked up individually from the floor and stuck into a block of 'Plasticine' on a table—the distances being the same each week. After a practice session the average time for three attempts was noted. He was also timed while climbing a flight of stairs and running a short distance on the level. Simple and discriminatory reaction times were measured as follows:

Simple Reaction.—The patient reacted to the lighting of an electric lamp by pressing a morse key. Each trial started with the hand on the key and only a slight downward pressure was needed to break the circuit.

Discrimination.—When one of 5 lamps was lit the patient pressed a corresponding key. Different bulbs were lit in random order. During a response the distance moved was the arm-reach of the patient when seated and without movement of his body as a whole.

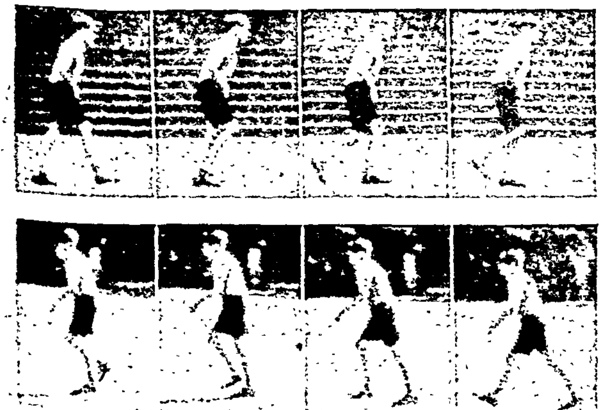

Fig. 2—Walking (above) before treatment and (below) during treatment with artane.

On each visit, 20 trials of each kind were made. The average time for 15 trials was recorded, the first 5 being disregarded.

Before each test the warning "Ready" was given. The lamp was lit after an interval which was varied between one and two seconds to prevent anticipation.

Reaction times were measured in hundredths of a second by a standard Electric Time Company chronoscope.

At the start of the tests the complete procedure was carried out twice so that he would have enough practice for the subsequent influence of learning on his speed to be negligible.

When treatment was altered, the change was always made on the day after testing.

The results of the tests were expressed graphically (fig. 1).

Without doubt the boy's condition was best when he was having artane. At other times, with the exception of the two weeks in which he received benadryl, he was listless, depressed, and self-conscious; the spasticity was worse, and insomnia and anorexia were more troublesome. During the four weeks on artane he was energetic and happy; he ate and slept well. The self-consciousness which had kept him indoors disappeared and he was at home only for meals. The drug very definitely relieved spasticity; the smile which had been so forced became natural and happy, and he swung his arms as he walked or ran (figs. 2 and 3). He was able to dress himself again after only two days' treatment, even to the extent of knotting his tie and tying his shoe-laces. Salivation was controlled, and he became more talkative. His speech itself was clearer.

Benadryl may also have improved his condition, but it seems unlikely that addition of amphetamine to artane did any good, and amphetamine alone was of little or no value. Apart from variations in tremor and muscle tone, there was little change in the neurological signs during the trial.

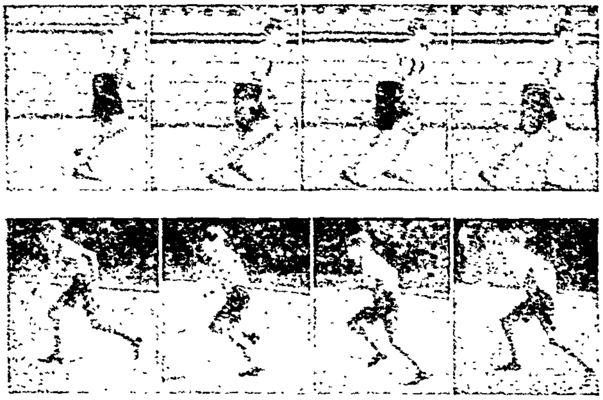

Fig. 3—Running (above) before treatment and (below) during treatment with artane.

After the experiment he was given 6 mg. of artane and 10 mg. of amphetamine daily. Owing to his summer holiday he was not seen again until Aug. 8 when his condition was both disappointing and puzzling.

Though his movements and tests were less satisfactory than during the trial period of artane, they were better than they had been before any treatment was given. His mother thought that there had been no physical deterioration, but it was clear that he was brooding a great deal on his physical handicap and on the failure of his hopes that the drug would restore him to his previous boisterous good health. He enjoyed quiet games with his friends, but returned home in despair when they played football for he was quite unable to keep pace for long and felt much inferior. He had become very self-conscious and thought he was being looked upon as a curiosity in the street or bus. No reversal of the sleep rhythm had been noted, but he was unable to sleep at night. He was also worried by his inability to go on with his classmates to the secondary school because his prolonged absence had prevented him sitting the necessary examination.

He had completely lost faith in his medicine and objected to continuing with it. In an attempt to show him its value treatment was stopped, with dramatic results (fig. 1). His *tremor became so bad that he was quite unable to pick up* pins. He was very stiff, and had to be pulled up from the sitting position. His gait, expression, and speech became much worse within twenty-four hours of stopping the drug. He lay in bed, anorexic, irritable, and depressed, apart from one occasion when he got up to look for his medicine.

Artane alone was restored after a week without treatment. Within twenty-four hours he improved dramatically and wanted to go to the pictures, which he was allowed to do. So far did the emotional pendulum swing with his release from incapacity, that a few days later he had to be rescued from a mechanical contraption, known as the "cake-walk" at the local fairground. The insomnia was completely relieved, his appetite returned, and he was again able to dress himself even to his tie and shoes. He rose early in the morning and began to take an interest in home hobbies.

He returned to school where he was happier because his teacher was a man who "did not fuss over him." His new teacher was successful in helping him to adjust himself to working in a class of younger children, and it has not been found necessary or considered advisable as yet to send him to a school for the physically handicapped.

At first a daily dose of 4 mg. of artane seemed to be too little, and 8 mg. too much; the optimum dose was 7 mg. The dosage has, however, been gradually increased to 10 mg. daily with benefit. After about three weeks of artane in full dosage he becomes rather dull and detached, though there is little change in the tests. He improves if the dosage is reduced to about 3 mg. daily for a few days.

DISCUSSION

During the epidemic of encephalitis lethargica thirty years ago the highest incidence was between the ages of 10 and 30, but old age and infancy were not exempt. The proportion of cases developing parkinsonism varied quite widely from one centre to another. But Parsons (1928) analysed a large number of cases and found that 6·5% of those under 16 and 6·9% of those over that age developed *parkinsonism, whereas conduct changes* were more than three times as common in the younger group.

The association between swimming and poliomyelitis aroused speculation as to whether this boy's visit to a swimming-pool had anything to do with his illness. He went swimming an apparently healthy boy and returned in a state from which he has not recovered. Perhaps trauma might have played a part, though there is no story of accident at the swimming-pool and the blow on the head came three days after the onset of symptoms. Patrick and Levy (1922), Kulkov (1932), Grimberg (1934), and Bruetsch and DeArmond (1935) are among those who have reported parkinsonism following cranial trauma, while Faure-Beaulieu (1932), Naville and de Morsier (1932), and Walker (1937) have described it after peripheral trauma. Though the latter has been disputed as a cause, it may bear some relation to the risk of prophylactic immunisation during an epidemic of poliomyelitis.

Using artane Doshay and Constable (1949) reported improvement in 76% of a series of cases of parkinsonism. Comparable figures published include 66% (Ellenbogen 1950), 80% (Phillips et al. 1950), and 74% (Garai 1951). The latter also found that 72% of patients improved on lysivane, though he felt in general that the improvement was somewhat greater with artane. Gallagher and Palmer (1950), on the other hand, thought lysivane the more effective of the two, "particularly in relieving the psychological symptoms." This view was also taken by Gillhespy (1951). Effron and Denker (1950) concluded that because of the great variation in the individual response of patients to the various drugs it was advisable to compare the effect of a number of them, either singly or in combination, in order to decide *which provides most relief in a given case.*

Attention has also been paid to the control of the associated emotional disturbances.

Bond and Appel (1931) described the good results obtained in a hospital school. The specialised staff "manifested optimism, an unemotional attitude, impersonal understanding, and coöperation. There was no spirit criticism, discipline, or punishment. The routine of th was not rigid, but followed regular schedules of rest, f exercise, duties in school, and play." The use of psychia methods showed that it was not the symptoms of behavi disturbances which were most important in these cases, b the underlying feelings of insecurity, the regressive tend and the intense extraversion and intraversion.

A drug which helps the patient by relaxing his tone is of course no cure for the underlying encephaliti which may smoulder for some years. It is quite however, *that without artane he is almost totally* incap-citated, whereas with it he is able to go to school and the less energetic games.

SUMMARY

After a visit to a swimming-pool, a boy of 11 de a vague illness, which was presumed to be enceph lethargica because it was followed by unmist parkinsonism. The effects of amphetamine, benadr and artane were studied. Artane was of definite and raised him from almost complete incapacity to restricted life.

I wish to express my thanks to Prof. R. W. B. Ellis permission to publish this case and for his advice; to Pr James Drever and Mr. R. L. Reid of the Department Psychology for their help in designing and carrying out measurement of the reaction times; to Miss D. W. Callow for her willing help in the dispensary; and to Lederle Labora-tories and Messrs. May & Baker for supplies of artane an lysivane respectively.

REFERENCES

Bond, E. D., Appel, K. E. (1931) Treatment of Behaviour Disord following Encephalitis. London.
Bruetsch, W. E., DeArmond, M. (1935) *J. nerv. ment. Dis.* 81, 53
Doshay, L. J., Constable, K. (1949) *J. Amer. med. Ass.* 140, 131
Effron, A. S., Denker, P. G. (1950) *Ibid*, 144, 5.
Ellenbogen, B. K. (1950) *Lancet*, i, 1034.
Faure-Beaulieu, M. (1932) *Pr. méd.* 40, 1327.
Ford, F. R. (1944) Diseases of the Nervous System in Infanc Childhood, and Adolescence. Springfield, Illinois.
Gallagher, D. J. A., Palmer, H. (1950) *N.Z. med. J.* 49, 531.
Garai, O. (1951) *Lancet*, i, 429.
Gillhespy, R. O. (1951) *Brit. med. J.* ii, 301.
Grimberg, L. (1934) *J. nerv. ment. Dis.* 79, 14.
Kulkov, A. E. (1932) *Ibid*, 75, 361.
Matheson Commission (1939) Report on epidemic encephaliti New York.
Naville, F., de Morsier, G. (1932) *Ann. Méd. lég.* 12, 165.
Parsons, A. C. (1928) *Rep. Publ. Hlth med. Subj., Lond.* 49, 1.
Patrick, H. T., Levy, D. M. (1922) *Arch. Neurol. Psychiat.* 7, 711.
Phillips, J., Montuschi, E., Sharkey, J. (1950) *Lancet*, i, 1131.
Walker, G. F. (1937) *Brit. med. J.* ii, 65.

STUDIES IN THE ÆTIOLOGY OF PNEUMONIA IN GLASGOW

1950-51

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APART from the report by Glover et al. (1948) there is little evidence of the extent to which the various ætio-logical agents are responsible for the pneumonia-like illnesses. It therefore seemed worth while to try to define more accurately the part played by the known pathogenic bacteria and viruses as causes of respiratory illness in patients admitted to hospital.

For many years cases notified as pneumonia have been admitted as a routine to certain wards in the infectious-

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* In receipt of a grant from the Medical Research Council.

BLE I—DISTRIBUTION OF CASES ACCORDING TO TIME AND METHOD OF INVESTIGATION

Period	Hospital	No. of cases		Special investigations
		Male	Female	
. 14, 1950– ept. 27, 1950	Knightswood	58	14	V*†
t. 28, 1950– arch 31, 1951	Knightswood	183 10	16 9	V + B* V†
v. 20, 1950– eb. 28, 1951	Ruchill	0	51	V

*V, Virological. *B, Bacteriological.
† Bacteriology limited to patients with pneumonia.

seases hospitals of the City of Glasgow. Indeed, the cility with which they are accepted has encouraged neral practitioners to interpret the diagnostic label of eumonia rather widely, with the result that patients ith a variety of acute and chronic respiratory diseases d their way into the wards. This was advantageous the present investigation, for it ensured that we were t dealing with a highly selected group of severely ill tients with pneumonia who had perhaps been sent to spital because they had resisted chemotherapy at me. Indeed, we found that between half and two-irds of the patients had not received specific therapy efore they reached hospital.

Material and Methods

eneral and Clinical

The patients form an almost continuous series admitted one male and one female ward in Knightswood Hos-ital and one female ward in Ruchill Hospital between anuary, 1950, and March, 1951. Complete bacterio-gical and virological examination of each case was not ossible throughout the entire period, but from October, 950, to March, 1951, every endeavour was made to void any omissions. Table I shows the distribution of ases according to the method of examination and ccording to sex.

A complete clinical examination was carried out shortly after admission; total and differential white-cell counts were made; and a postero-anterior radiograph was taken. The following diagnostic definitions were adopted:

Febrile Catarrh.—An acute illness characterised by fever and symptoms of upper respiratory-tract infection but without clinical or radiological evidence of bronchitis, pneumonia, or other pulmonary lesion.

Bronchitis.—Acute bronchitis or acute exacerbation of chronic bronchitis with no clinical or radiological evidence of pneumonic consolidation.

Pneumonia.—This diagnosis was made in the first instance from the clinical examination and in every case was confirmed radiologically. The bacteriological examination of sputum and blood from these cases was usually fairly complete except when specimens were unobtainable—for example, because of death shortly after admission.

Congestive Cardiac Failure.—These patients presented the usual signs of cardiac failure without evidence of pulmonary consolidation, clinically or radiologically.

Miscellaneous.—This comprised a wide variety of diseases mainly affecting the respiratory tract—e.g., tuberculosis, pleurisy with effusion, and bronchial carcinoma—but including such conditions as rheumatic carditis and transverse myelitis.

Bacteriological

As soon as was convenient after admission a specimen of sputum was obtained and blood was withdrawn for culture. The sputum, after emulsification of a suitable portion, was cultured on blood-agar plates, and a sample was injected intraperitoneally into a mouse. Cultures were examined next day, and when the mouse was sick or dead its peritoneal exudate was examined for the presence of pathogens. If pneumococci were identified they were typed. Blood-cultures were incubated aerobically and examined at the end of twenty-four and forty-eight hours. When, for any resaon, sputum was unobtainable, postnasal and throat swabs were usually taken and examined in a similar fashion.

Virological

Although virus isolation from gargling was attempted from selected cases, the identification of a virus infection depended mainly on the demonstration of antibodies in the patient's serum. For this purpose, therefore, blood was removed by venepuncture on admission or within twenty-four hours thereafter, and a second specimen was obtained about the fourteenth day of illness (usually from seven to ten days after admission to hospital). These specimens of blood were allowed to stand at 37°C until the serum had separated. Samples were stored in the refrigerator at +4°C until the tests were made. These paired samples of blood-serum were examined for the presence of cold agglutinins, *Streptococcus MG* agglutinins, complement-fixing and hæmagglutination-inhibiting antibodies against influenza viruses A and B, and complement-fixing antibodies for psittacosis virus and *Rickettsia burneti.*

The serological methods used were based on those in current use at the Virus Reference Laboratory, Colindale.

The tests for cold agglutinins followed the technique of Feller (1948). *Strep. MG* agglutinins were determined in four serial dilutions of serum (from 1 : 10 to 1 : 80) by overnight incubation at 37°C. Influenza virus A and B soluble antigens were prepared by the method described by Stoker and Marmion (1950) for use in complement-fixation tests. In testing, all dilutions were made in barbiturate-buffered calcium magnesium saline solution; each tube contained 0·1 ml. each of serum dilution, optimal antigen dilution, and 2·5 minimal hæmolytic dose (M.H.D.) of complement; fixation was for one hour at 37°C, with a further half-hour's incubation after the addition of 0·2 ml. of 2·5% sensitised sheep cells per tube. Conventional controls were included and fixation recorded in the usual way, less than 50% hæmolysis being regarded as positive. Influenza hæmagglutination-inhibition tests were made in tubes by the Salk (1944) method, using 0·125% final concentrations of human group-O cells and four hæmagglutinating units of virus in 0·6 ml. final volumes. The viruses used were elution-purified A (PR8), A prime (1949, Paris), and B (Lee) strains. Psittacosis complement-fixation tests followed the technique of Dr. A. D. Macrae (personal communication), who supplied boiled antigens prepared from infected yolk sacs (Bedson et al. 1949). The method was essentially similar to that for influenza, except that dilutions were made in saline solution and 2 M.H.D. complement and 1% sensitised cells were used. The examinations for Q fever were made at the Virus Reference Laboratory, Colindale.

The complement-fixation tests on eighteen alternate sera obtained at the beginning of the study were made by similar methods by Dr. R. H. Swain, of Edinburgh University bacteriology department.

Results

It has already been explained that the 341 patients can be divided into two groups. In one of these, both bacteriological and virological results are fairly complete; in the other, virological investigations are again fairly complete, but bacteriological investigations are confined to the cases of pneumonia admitted to Knightswood Hospital. We shall begin by describing the results in the 199 patients where the examinations were complete, and shall then describe the results of the series as a whole.

CASES WITH COMPLETE EXAMINATION

From October, 1950, to March, 1951, 199 patients were admitted. Their ages ranged from 13 to 84, and all but 16 were male. The final clinical diagnoses were: pneumonia 129, bronchitis (acute and chronic) 28, febrile catarrh 6, congestive cardiac failure 10, and miscellaneous 26.

Table II shows the results of the bacteriological examinations. From the 129 patients with pneumonia a pneumococcus was isolated in 84 (65%). All the pneumococci could be typed, and types 1–8 accounted for 62

TABLE II—DISTRIBUTION OF 199 CASES BY CLINICAL DIAGNOSIS AND RESULT OF BACTERIOLOGICAL INVESTIGATION

Clinical diagnosis	Bacteriology				Total
	Pneumococcus types 1–8	Pneumococcus types 9, &c.	Other pathogenic bacteria	Undetermined	
Pneumonia	62	22	10	35	129
Bronchitis	6	10	0	12	28
Febrile catarrh.. ..	0	1	0	5	6
Cardiac disease ..	0	3	0	7	10
Miscellaneous conditions	4	6	1	15	26
Total	72	42	11	74	199

Patients from whom more than one pneumococcus type was isolated have been included once only—under the lowest recorded type.

(11 of type 1, and 26 of type 2). Bacteria which could be assumed to be pathogenic (e.g., *Staphylococcus aureus*) were isolated from a further 10 patients. Examination of the remainder (35 patients) failed to elicit a pathogenic agent, and the cultures of sputum yielded a mixed normal flora. From the 70 patients whose pneumonia was not confirmed, pneumococci were isolated from 30 (43%), and types 1–8 accounted for 10 of these. From 39 of the remaining 40 patients culture of the sputum yielded a normal mixed flora. These results are what would be expected. The significantly higher proportion of pneumococcal infections in those patients with pneumonia is not perhaps surprising, although it had been thought that a higher proportion of "other pathogens" might have been encountered in the miscellaneous non-pneumonic group. It must be admitted that, in the absence of bacteriæmia or other proof of systemic invasion, the exact significance to be apportioned to the higher types of pneumococci is conjectural. In many instances the leucocytosis with well-marked preponderance of polymorphonuclears supported the view that the cause was bacterial.

Table III shows the correlation between the bacteriological and the serological findings in this completely examined group. It will be observed that in the proportions with positive serological findings there is some variation between the different clinical subgroups; but none of these differences is great, and the small numbers in some of the subgroups make comparison difficult. Of the patients with pneumonia 31 (24%) gave positive findings whereas in the non-pneumonic group the figure was 28 (40%). This difference is not formally significant.

TABLE III—RESULTS OF SEROLOGICAL TESTS IN 199 BACTERIOLOGICALLY EXAMINED CASES

Serological correlations	Pneumonia				Bronchitis	Febrile catarrh	Cardiac	Miscellaneous	Total
	Pneumococcus types 1–8	Pneumococcus types $\geqq 9$	Other bacteria	Undetermined					
With influenza-A infection	5	2	1	4	4	3	0	3	22
With recent influenza-A infection	7	3	5	4	9	1	1	5	35
With cold agglutinins	0	0	0	0	0	0	0	2	2
With previous infection with ornithosis or lymphogranuloma venereum	1	1	0	0	0	0	0	1	3
Without positive serological tests	49	16	4	27	15	2	9	15	137
Total	62	22	10	35	28	6	10	26	199

It will also be observed that all but 2 of the serological findings were obtained with infl antigens. The negative results with most of the logical tests have encouraged us to pay more att to the description of the results in the whole series, a decision might have had inherent dangers had th been, for example, positive reactions to the cold-agglutinin or *Strep. MG* agglutination tests. It may reasonably be assumed that the bacteriological results in the wh series would have followed a similar pattern to found in the group of 199 patients. We feel that the results should be recorded separately so that subsequent tions may be made to them, by ourselves or others meanwhile we omit detailed analysis of this rather group and proceed to examine the series as a whole.

SERIES AS A WHOLE

In assessing the results of serological examination lowest titres (expressed as reciprocals of serum dil accepted as significant in single tests were as cold agglutinins 64; *Strep. MG* agglutinins 40; p cosis complement-fixation test 40, and influenza plement-fixation test 16. A fourfold or greater rise titre during the illness was accepted as signifying that the illness was associated with infection by the corresponding agent. The results of the serological examinations in relation to the admission dates of the cases are shown in the accompanying figure. It will be seen that the positive results obtained from the different tests, apart from influenza, were few and occurred sporadically. Significant reactions with influenza-B antigen were obtained during January and March, 1950, and influenza-A reactions were detected from December, 1950, to March, 1951. In January, 195 paired sera from 2 patients showed barely significant increases in titre in single tests with influenza-A antigens; insufficient sera for confirmation were available, and the cases therefore have not been accepted as definite influenzal infections. Both were lobar pneumonias, from which pneumococcus type 25 was isolated from the sputum in one, and pneumococcus type 2 in the other.

TABLE IV—RESULTS OF SEROLOGICAL TESTS: TOTAL

Nature of test	316 cases with paired sera			23 cases single sera	
	No. tested	No. positive		No. tested	No. positive
		Fourfold rise	Other*		
Cold agglutination ..	297	1	1	10	0
Strep. MG agglutination	258	0	0	10	0
Psittacosis complement-fixation test	309	2	2	13	1
Influenza complement-fixation test	268	31	52	21	5
Influenza Salk test ..	230	22	0	0	0

* Significant titre in one or both sera, but no fourfold rise in titre.
Two cases omitted from table where virus isolation alone was attempted.

The results of the various tests in relation to the number performed are shown in table IV. It will be more convenient if each of these tests is taken singly.

Cold Agglutinins

Only 2 (0·7%) patients showed cold agglutinins in significant titres.

The first was a man, aged 74, with titres of <8, 64, and on the 3rd, 14th, and 22nd days of illness. The pneumonia in this case was complicated by myocardial degeneration. *Strep. MG* agglutinin titres remained under 10, and all other tests were negative. Radiologically there was a left basal consolidation, but no bacterial pathogens were isolated from the sputum.

e second patient, a man aged 28, gave titres of 256 and 16 e 14th and 28th days of illness. Clinically it was con- ed that resolution was already advanced on admission to ital, but radiography did not confirm the presence of olidation. *Strep. MG* titres were 10 and 10. All the r tests were negative. No bacterial pathogens were ted from the sputum.

ptococcus MG Agglutination Tests

o significant reactions were detected, and only in ases were titres as high as 10 or 20 obtained.

lacosis Complement-fixation Tests

should be emphasised that the group antigen used ese tests does not distinguish between infections due e different viruses of the ornithosis-lymphogranuloma ip.

ne patient, a man aged 60, showed a fourfold rise in titre : lings of 80, 320, and 320 on the 7th, 16th, and 153rd days r the onset of illness. Clinically the picture was that of umonia of the left lower lobe. Leucocytosis was absent ite cells 9000 per c.mm.). No bacterial pathogens were ated on culture of the sputum or after intraperitoneal ction of a mouse. Prompt recovery followed aureomycin itment. Examination of the patient's wife and son did reveal clinical or serological evidence of infection. In of recent contact with breeding pigeons, infection with a on strain of ornithosis virus seemed likely.

woman, aged 75, admitted in cardiac failure, gave titres <8 and 20 on the 32nd and 39th days of her fatal illness. later specimens of serum were available for comparison, this low rise in titre late in the course of illness was bably of non-specific origin.

A third patient, admitted twice during the period of the estigation, showed unchanging titres of 40 in all serum nples examined. Forty years previously he had been in con- t with pigeons for several years and nursed a sick budge- ar until its death. He was aware of no illness at that time.

A single serum from a fourth patient, who died from ncreatic carcinoma, also gave a titre of 40.

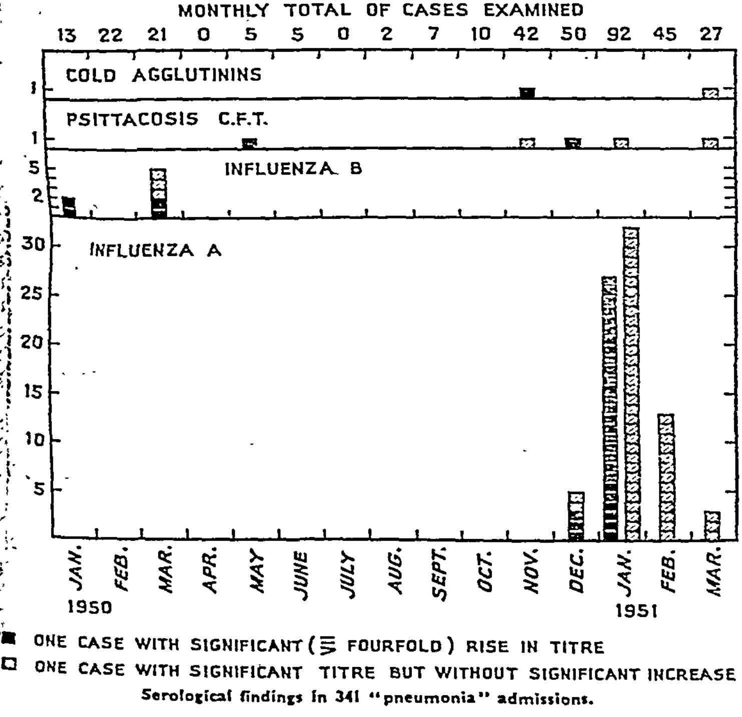
Previous infection with some virus of the ornithosis- nphogranuloma group is the likely explanation of the rological reactions of these last two cases.

TABLE V—ANALYSIS OF SEROLOGICAL TESTS FOR INFLUENZA IN WHOLE SERIES

Results of tests	Clinical and bacteriological diagnosis						Total
	Pneumonia			Bronchitis	Febrile catarrh	Miscellaneous	
	Pneumococcal	Bacterial non-pneumococcal	No bacterial pathogen identified				
Fourfold rise in titre (Salk or complement-fixation test)	7	2	8	7	6	4	34
Complement-fixation test titre ⩾ 16	10	3	14	13	1	8	49
Complement-fixation test titre < 16	92	7	58	22	6	36	221
Total no. serum-pairs tested	109	12	80	42	13	48	304
Single serum complement-fixation test titre ⩾ 16	1	2	0	0	0	1	4
Single serum complement-fixation test titre < 16	3	0	5	2	0	8	18
Not tested	3	0	7	1	1	3	15
Total	116	14	92	45	14	60	341

fluenza

In the diagnosis of influenza, complement-fixation sts with soluble antigen not only reveal active infections hown by rising titres) but also allow the detection of recent infections by the presence of significant but static or falling titres. Titres of 16 or more were found in this study only during and shortly after the two periods when active infections with the corresponding virus were known to be occurring in the country. The interpretation of the Salk test is rendered more difficult by the occurrence of non-specific inhibition of hæmagglutination, and significance was ascribed only to fourfold or greater rises in titre indicating active infection. Good agreement between the two methods was found in the diagnosis of such active infections. Thus, during the six weeks in which alone cases of active influenza-A infection were detected in this series (Grist 1951), of 66 patients examined by both techniques 21 showed a fourfold or greater rise in titre by the Salk test, 19 by complement-fixation, and 17 by both methods. Of the Salk tests in this same group 17 were positive using 1949 A prime virus, 13 using PR8, and 9 with both strains. It was at first surprising that the average rise in hæmagglutination-inhibiting titre shown by our cases during the epidemic was little higher against the presumably closely related A prime virus than against the relatively distant PR8 strain. However, the A prime strain used in the test was subsequently found by Isaacs and Andrewes (1951) to be in the relatively insensitive Q phase.



Serological findings in 341 "pneumonia" admissions.

The results of serological tests for influenza infection in relation to the various diagnostic categories are shown in table V. It will be observed that similar proportions of positive cases occurred among the pneumococcal pneumonias and those from whom no bacterial pathogen was isolated. The slightly higher proportions found in the groups of non-pneumococcal bacterial pneumonia, bronchitis, and respiratory catarrh are explained by the fact that an excess of these groups was examined during the influenza epidemic. Indeed, most of these positive serological reactions for influenza were obtained during the

TABLE VI—SEROLOGICAL TESTS FOR INFLUENZA DURING "EPIDEMIC" PERIOD FROM DEC. 25, 1950, TO FEB. 4, 1951

Results of tests	Clinical and bacteriological diagnosis –							Total
	Pneumonia				Bronchitis	Febrile catarrh	Miscellaneous	
	Pneumococcal types 1–8	Pneumococcal types $\geqq$ 9	Bacterial non-pneumococcal	No bacterial pathogen identified				
Fourfold rise in titre (Salk or complement-fixation test)	5	2	1	8	7	3	4	30
Complement-fixation test titres $\geqq$ 64	4	1	1	6	8	1	2	23
Complement-fixation test titres > 16 < 64	2	0	2	2	1	0	1	8
Complement-fixation test titres <16	3	3	1	11	4	2	8	32
Total no. serum-pairs tested	14	6	5	27	20	6	15	93
Single sera $\geqq$ 16 ..	0	1	2	0	0	0	0	3
Single sera <16 ..	0	1	0	3	1	0	3	8
Not tested	0	0	0	1 (anti-complementary)	0	0	0	1
Total	14	8	7	31	21	6	18	105

epidemic period of winter 1950–51, and a clearer picture of the rôle of influenza is obtained by considering in more detail the patients admitted during this six-week period alone. Table VI shows that during this period about two-thirds of all admissions gave some evidence of infection with influenza-A virus. The figures are, of course, too small to show minor differences, but no gross inequality is apparent between the proportions of "influenzal" cases in the different groups. When the pneumococcal pneumonias are separated into those patients affected by the lower, and those affected by the higher, pneumococcal types, no significant difference emerges. Type-2 pneumococcus, which is the type most often encountered in Glasgow among patients with pneumonia, was responsible for 7 infections, of which 3 showed a fourfold rise in titre and 1 gave titres of 16 in both sera. When the results in all of the pneumonia patients are considered, it is found that in 31% influenza infections were "synpneumonic" (as judged by fo or greater rises in antibody titres) and in 23% it considered recently "prepneumonic" because of presence of titres of 64 or more on admission. Most patients who gave relatively static titres of 16 or were encountered during the later weeks of the infl outbreak. It may also be noted here that the distributions of influenzal and non-influenzal cases not differ significantly.

It is of interest that no fulminating cases of comb staphylococcal and influenza-virus pneumonia encountered during the present series, although a cases clinically and bacteriologically of this pattern known to occur in Glasgow during the winter. In bias might have arisen from the presence in the seri patients who died before the development of diag titres of influenzal antibody, it was considered desi to examine specially the patients who had died the epidemic period of six weeks and the sub period. The bacteriological and serological findings tabulated in table VII. From most of these patients o one admission serum sample was available, and in 3 of them did the titre attain significant levels. A from the expected frequency of the combination bronchopneumonia and cardiac failure the table d not reveal the dominance of any particular clinical bacteriological entity associated with mortality or after the influenza-A epidemic. Examination of th cases from the same series and period (table VIII) fr whose respiratory tracts strains of *Staph. aureus* w isolated also does not bring to light any dominant dise entity. Case 213, a patient who was severely ill admission to hospital and showed high influenza anti *titres, most nearly resembles the fulminating type of*

The range of conditions associated with equi simultaneous influenza-A infection found during th epidemic period is shown in table IX. Of the 5 ca grouped together under the heading of influenza, 3 w straightforward cases of clinical influenza. The other gave very large titre rises against influenza-A antigens both Salk and complement-fixation tests:

One, a man aged 75, was admitted on the 7th day of illr with clinical evidence of bronchopneumonia. Radiol all increased lung markings were observed. The sputum sh a normal respiratory flora. A small effusion developed befo recovery ensued.

The other, aged 66, was admitted on the 2nd day of illn and presented a picture of hypertensive cardiac failure considerable moisture in both lungs. Radiologically, increase lung markings were again seen, and the sputum again con tained a normal mixed bacterial flora.

Out of all the 30 cases with active influenza infection the 2 approximate most closely to the picture of vir

TABLE VII—KNIGHTSWOOD DEATHS DURING EPIDEMIC AND POST-EPIDEMIC PERIODS

Period	Case no.	Diagnosis	Bacteriological findings (respiratory)	Influenza-A complement-fixation test titres*
Epidemic ..	169	Respiratory catarrh and cardiac failure	No pneumococcus isolated	<4/<4
	172	Pneumonia and cardiac failure	No pneumococcus isolated	<4/<4
	173	Cardiac failure and chronic bronchitis	Pneumococcus type 20	<4
	183	Bronchopneumonia	Pneumococcus type 22	8
	187	Chronic bronchitis and cardiac failure	[illegible]	8
	198	Bronchopneumonia and cardiac failure		64
	226	Bronchopneumonia	.. .	Paired sera, anti-complementary
	227	[illegible]	β hæmolytic streptococcus, proteus, *Staph. albus*	64
	235	[illegible] bronchitis	..	<4
	249		..	<4
Post-epidemic	255	Pneumonia and lung abscess	Pneumococcus type 3, Friedländer's bacillus	<4
	275	Pneumonia and intestinal obstruction	..	8
	276	Bronchopneumonia	Mixed normal flora	No serum obtai
	284	Bronchopneumonia and cardiac failure	Mixed normal flora	<4/<4
	287	Miliary tuberculosis	Mixed normal flora	32
	291	Pancreatic carcinoma	Pneumococci types 3, 5, 12	<4
	294	Acute laryngotracheobronchitis	Pneumococcus type 3	8
	301	Cardiac failure	No pneumococcus isolated	8
	302	Bronchopneumonia and tuberculosis	*H. influenzæ* and coliforms	8
	306	Cardiac failure	No pneumococcus isolated	<4

* In most cases only one admission serum specimen was available; where two sera were tested, titres are separated by an oblique stroke

amonia and bear some resemblance to the group-B s of Scadding (1937).

ever

hrough the kindness of Dr. B. P. Marmion 76 specis of serum were examined for the presence of ibodies to *R. burneti*. The results were all negative.

Discussion

rom the data presented above there emerges no gnisable picture of respiratory disease characterislly associated with influenza-virus infection. The ilarity of the proportions in the different disease cateies of cases reacting significantly in tests for influenzaas infection almost suggests that the occurrence of uenza was a chance phenomenon. But, although re are no figures to support such a belief, it seems at st surprising that two-thirds of the population of asgow should have suffered infection by the influenza irus. It seems possible that different parts of the ountry varied considerably in the incidence of influenza. t is difficult to obtain figures to support such a view, ut at the Royal Society of Medicine discussion on nfluenza in 1951 the attack-rates were estimated for lifferent groups at 6% at Coventry (Massey 1951) and 5·6% at Salford (Burn 1951).

BLE VIII—CASES WITH *Staph. aureus* IN SPUTUM DURING EPIDEMIC AND POST-EPIDEMIC PERIODS

riod	Case no.	Diagnosis	Influenza-A complement-fixation test titres
idemic	208	Pneumonia rt. base, resolving ..	32/16*
	213	Pneumonia lt. middle lobe	128/128
	216	Rt. pneumonia and lung abscess ..	8/8
	248	Bronchopneumonia	16/32
Post-idemic	253	Tuberculosis	8/4
	265	Pneumonia rt. base (pneumococcus type 2)	<4/<4
	280	Pneumonia and septicæmia (pneumococcus type 13)	<4/<4

In each case the oblique stroke separates the acute and convalescent titres.

The high proportion of patients whose sputum did not reveal the presence of pathogenic organisms is also urprising. In a fair proportion of these patients the clinical, radiological, and hæmatological evidence all upported a view that the illness was bacterial in origin. This experience is new; for there is little doubt that, before the introduction of chemotherapy, known pathogens could be isolated from the sputum of the great majority of cases of pneumonia. Anderson (unpublished data) studied a series of 500 patients between 1939 and 1941 and encountered only 8 from whom pathogens were not obtained. However, Stuart-Harris et al. (1949) have also recorded finding a high proportion of pneumonia admissions with a normal bacterial flora in the sputum. Whether this may be associated with chemotherapy before admission to hospital is worthy of investigation.

The last point, which is perhaps of some importance, is that, apart from the presence of influenza-virus infection during an epidemic period, this series of consecutive cases shows little evidence of the presence of known virus infection. The small proportion of positive results obtained in the cold agglutination and *Strep. MG* agglutination tests shows that cases of so-called primary atypical pneumonia are not often admitted to the Glasgow hospitals. It is interesting that this finding is in agreement with that of Glover et al. (1948), who approached the problem in a different way. So far as Glasgow is concerned, the explanation of this is not likely to lie in the fact that such cases do not gain admission to hospital because of their mildness, for many of the cases admitted to the present series were not of great severity. Further, the diagnostic label of virus pneumonia, applied (as it often is) on purely clinical grounds, sometimes implies a somewhat severe and bizarre type of illness; and if such cases were occurring in Glasgow we might have expected to find some in the present series. In our opinion the diagnosis of virus pneumonia unsupported by any laboratory evidence is quite unjustified. The present series of cases suggests that, apart from the increased prevalence of pneumonia, which is a natural accompaniment of an influenza epidemic, known viruses play little part in the ætiology of pneumonia. This statement must not be taken to suggest that some viruses, as yet unknown, may not have an important rôle in the initiation of the pneumonic infection, but merely emphasises that, in the great majority of pneumonias, a bacterial ætiology may be inferred.

TABLE IX—RANGE OF CONDITIONS ASSOCIATED WITH SIMULTANEOUS INFLUENZA-A INFECTION

Diagnosis		No. of cases	Total
Bacterial pneumonia	Pneumococcus 1–8	5	
	Pneumococcus ⩾ 9	2	
	β hæmolytic streptococcus	1	
	Normal flora	6	14
Acute exacerbation of chronic lung disease	Bronchitis	7	
	Bronchiectasis	1	
	Tuberculosis	1	9
Influenza	Uncomplicated	3	
	Bronchopneumonia	2	5
Miscellaneous ..	Dry pleurisy	1	
	Cardiac failure	1	2

Summary

During a period of fifteen months the patients admitted to the pneumonia wards of two Glasgow fever hospitals were studied in regard to the bacterial and viral ætiology. In a group of patients whose laboratory investigations were complete no evidence was obtained that a particular clinical picture was associated with virus infection. Of the whole series of 341 patients, 2 had raised levels of cold agglutinins, and none showed the presence of *Strep. MG* agglutinins to a significant degree. On serological evidence 1 patient was diagnosed as having ornithosis, and in 2 patients evidence of previous infection with ornithosis viruses was obtained. From January to March, 1950, a few cases of influenza-B infection were diagnosed, and during the winter epidemic of 1950–51 a considerable number of infections with influenza A were detected.

105 patients were admitted during the period of the influenza-A epidemic, and about two-thirds of these showed serological evidence of influenza-A virus infection. Influenza-virus infection was not associated with any characteristic pattern of illness, and no cases of fulminating combined staphylococcal and virus pneumonia were encountered.

It is considered that few cases of serious respiratory illness in Glasgow are attributable to a virus, apart from the increased prevalence of respiratory infection which accompanies an influenza epidemic. The diagnosis of virus pneumonia made without supporting laboratory evidence seems inadmissible.

For their advice and help in various aspects of these studies we wish to thank Dr. C. H. Andrewes, of the World Influenza Centre; Prof. D. F. Cappell, of the department of pathology in the University of Glasgow; Dr. F. O. MacCallum, director, and Dr. B. P. Marmion and Dr. A. D. Macrae, of the Virus Reference Laboratory, Colindale, London; Prof. C. H. Stuart-Harris, of Sheffield; and Dr. R. H. Swain, of the department of bacteriology in the University of Edinburgh. We also acknowledge the assistance of the resident medical staffs of Knightswood and Ruchill Hospitals, and in particular that of Dr. A. M. T. Drimmie, Dr. M. B. Eadie, and Dr. M. McLeod.

REFERENCES

Bedson, S. P., Barwell, C. F., King, E. J., Bishop, L. W. J. (1949) *J. clin. Path.* 2, 241.
Burn, J. L. (1951) *Proc. R. Soc. Med.* 44, 801.
Feller, A. E. (1948) *In* American Public Health Association. Diagnostic Procedures for Virus and Rickettsial Diseases. Chicago.
Glover, R. E., Humphrey, J. H., Joules, H., Van der Walt, E. D. (1948) *Thorax*, 3, 214.
Grist, N. R. (1951) *Proc. R. Soc. Med.* 44, 798.
Isaacs, A., Andrewes, C. H. (1951) *Brit. med. J.* ii, 921.
Massey, A. (1951) *Proc. R. Soc. Med.* 44, 790.
Salk, J. E. (1944) *J. Immunol.* 49, 87.
Scadding, J. G. (1937) *Brit. med. J.* ii, 956.
Stoker, M. G. P., Marmion, B. P. (1950) *Brit. J. exp. Path.* 31, 332.
Stuart-Harris, C. H. S., Laird, J., Tyrrell, D. A., Kelsall, M. H. Franks, Z. C., Pownall, M. (1949) *J. Hyg., Camb.* 47, 434.

CAT-SCRATCH FEVER

A CASE IN ENGLAND

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THE case of cat-scratch fever reported here seems to be the first recorded in England, though the condition is well known in France (Debré et al. 1950, Mollaret et al. 1950, THE LANCET 1950) and has lately been shown to be widespread in America (Daniels and MacMurray 1951, THE LANCET 1952).

A married woman, aged 34. In the last week of September, 1951, her kitten was taken ill; while holding the animal for the vet to examine it, the kitten bit her moderately deeply on the dorsum of her left hand, producing a wound about $^3/_4$ inch long. This was immediately treated with an antiseptic and seemed to heal normally in the next 10 days. The kitten, however, died a few hours after inflicting the bite, the cause of death being unknown.

The patient remained well until Nov. 2, when she had a general headache all day. Next day she complained of muscular aching and had a few rigors, followed by a persistent "curious aching pain in the back of the chest," aggravated by breathing; she had no cough, but an erythema appeared all over her trunk for a few hours. On the 4th her temperature rose to 100°F and she retired to bed because the headache and muscular pains were worse. Her temperature was 101° on the 5th, when her symptoms were still increasing. On the 6th her temperature was 102° and the headache and muscle pain were severe.

On Nov. 7, when she was first seen by the writer, her temperature was 99°; her general condition was good and no rash was now present. Her tongue was furred but the throat was clean. The only enlarged lymph-glands were the left epitrochlear, which was the size of a walnut, firm and tender, with slight reddening of the overlying skin, and the left axillary, slightly. The scar of the bite was clearly seen on the back of her left hand; though it had apparently healed, the wound was unusually purplish and a little indurated. There was no sign of pus formation. All other systems were normal. Blood-pressure 130/80 mm. Hg. She was given 1 g. of chloramphenicol on Nov. 8, followed by 0·5 g. four-hourly until the 12th, when the dosage was reduced to 0·5 g. six-hourly; the drug was stopped on Nov. 15.

Investigations

Hæmoglobin, white-cell count, and differential count normal.

Paul-Bunnell reaction negative.

Blood-films examined for spirilla: none found.

Blood-serum sent to Wellcome Laboratories of Tropical Medicine for agglutination-tests against *Leptospira ictero-hæmorrhagiæ* and *L. canicola*: both were negative in all dilutions.

Blood-cultures were put up in 'Liquoid' broth and subcultured on blood-agar, but on incubation aerobically, anaerobically, and in CO_2 no organisms were grown.

Subsequent Course

On Nov. 24, since there had been no response to chloramphenicol and the epitrochlear gland was enlarging, she was started on penicillin 500,000 units twice daily, on the assumption that she might have rat-bite fever (the house harboured rats), but there was no response to a seven-day course. F this time, however, her temperature slowly returned to n

During the next fortnight a tiny bead of pus app under the edges of the original wound. Attempts to cul an organism from this failed.

By Dec. 13 the left epitrochlear gland was obvi softening and about 1 ml. of thick fluid was aspirated from Direct examination of this material revealed many po morphs but no acid-fast bacilli. A moderate growth micrococci was obtained from enrichment culture only. mouse injected intraperitoneally with the material on De and killed on the 20th showed no evidence of infection *Spirillum minus* or pasteurella. A guineapig was injected the same time and killed on March 3, but no evidence disease was found at necropsy.

Skin-test

At this time the series of cases in the U.S.A. was repo by Daniels and MacMurray (1951), who very gene supplied some antigen (Franzoni), made from a typical ca cat-scratch fever, which had produced a definite skin-re in two other cases. The patient was injected intraderma with 0·1 ml. of this antigen on her forearm, her hus receiving a similar injection as control. After 24 hours patient showed a minute papule surrounded by a zone erythema $^1/_8$ inch in diameter; at 48 hours the papule its measured $^1/_8$ inch across while the erythema was $^1/_4$ inch diameter. The control injection produced no reaction at

The clinical picture and course of this case, with t positive skin-reaction, seem to make the diagnosis cat-scratch fever virtually certain. The causati organism, almost certainly a virus, remains to isolated, though its transference to anthropoids (Dan and MacMurray 1951) has recently been reported.

It is a pleasure to thank Dr. J. Hedley Cule, the pati general practitioner, who has been of the greatest assis throughout; Dr. J. V. Barker, assistant bacteriologi King's College Hospital, for the many bacteriological inv gations; and the Wellcome Laboratories of Tropical Medi for some of the agglutination reactions.

REFERENCES

Daniels, W. B., MacMurray, F. G. (1951) *Arch. intern. Med.* 88,
Debré, R., Lamy, M., Jammet, M. L., Costil, L., Mozziconacci,
(1950) *Bull. Soc. méd. Hôp. Paris,* 66, 76.
Lancet (1950) Annotation, ii, 812.
— (1952) *Ibid,* i, 302.
Mollaret, P., Reilly, J., Bastin, R., Tournier, P. (1950) *Pr. méd.* 1353.

Preliminary Communication

EFFECT OF A.C.T.H. ON HAIR GROWTH IN ALOPECIA AREATA AND UNIVERSALIS

NUMEROUS endocrine substances have been used wit out success in the treatment of alopecia areata[1,2] ar there is little evidence that alopecia of this type associated with any disorder of internal secretion. Clinical evidence suggests that hyperadrenocortic syndromes show a reduced hair growth on the scal and adrenocorticotrophic hormone (A.C.T.H.) has be found to inhibit hair growth in rats.[6,7] In spite of t discouraging evidence, however, I have used A.C.T in four cases of alopecia.

Of the four patients, three had had alopecia univers for 1–3 years, and since the complete loss of hair th had been no recent partial remission. Two were adu and one was a girl aged 9 years. The fourth pati also a girl of 9, had had severe partial alopecia for year, with spontaneous exacerbations and remissio All three patients with alopecia universalis had a histo of allergic manifestations, such as eczema and asthm but in only one were these severe. The girl with part alopecia had no history of allergy.

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1. Walker, S. A., Rothman, S. *J. invest. Derm.* 1950, 14, 403.
2. Rony, H. R., Zakon, S. J. *Arch. Derm. Syph.* 1945, 52, 323.
3. Waisman, M., Kepler, E. J. *J. Amer. med. Ass.* 1941, 116, 2
4. Danforth, C. H. *Physiol. Rev.* 1939, 19, 94.
6. Selye, H. Textbook of Endocrinology. Montreal, 1949; pp. 1 169.
6. Butcher, E. O., Richards, R. A. *Endocrinology,* 1939, 25, 75
7. Baker, B. L., Whitaker, W. L. *Anat. Rec.* 1948, 102, 333.

TREATMENT AND RESULTS

hods

o the adults A.C.T.H. was given intravenously in a 5% ose drip running for twelve hours daily. The dose ed between 15 and 20 mg. To the children A.C.T.H. given intramuscularly in a dosage of 40–60 mg. y in four divided doses. Observations on the four ents included:

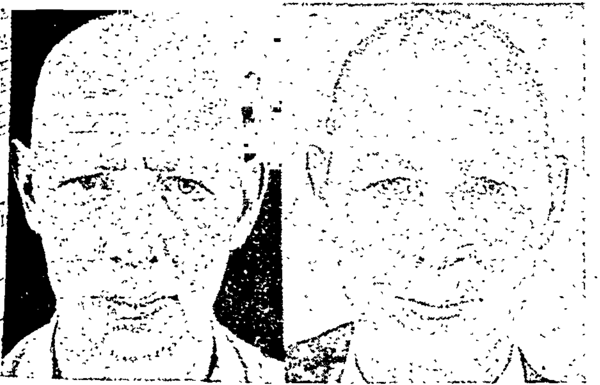
) A daily measurement of blood-pressure, body-weight, fluid balance.

) A twice-weekly estimation of blood levels of proteins, lesterol, sodium, potassium, and chlorine, and of the li reserve.

) A weekly complete blood-count, a total eosinophil- nt, and an estimation of the erythrocyte-sedimentation .

ll-thickness biopsy of the scalp was done before, ing, and after treatment. Treatment usually lasted m six to eight weeks. Benign symptoms of intolerance re usually noted after three or four weeks' treatment. this time dosage was sometimes reduced or was netimes combined with other agents.

In the three cases of alopecia universalis hair began grow in 8–10 days and there was quite a satisfactory owth by 21 days. The accompanying figure illustrates e hair growth in case 2; and when the second photo- aph was taken this patient was shaving daily. After is treatment period of about 21 days there was a riking growth of hair mainly confined to the scalp, beard, and eyebrows. Initially this was a soft downy growth but later it became natural pigmented scalp and facial hair. Hair growth continued while the adrenal stimulation by A.C.T.H. was maintained. However, when the A.C.T.H. dosage was reduced below a critical level or stopped, the hair began to lose its lustre and in about 10 days became loose and began to fall out. The patient's condition then returned to one of total alopecia after about 18–21 days without treatment.


Before treatment with A.C.T.H. (July 27, 1951). After treatment (Oct. 2, 1951).

In the one case of partial alopecia there was a similar growth of hair, *covering the bald patches, but the hair* continued to grow after cessation of treatment and is still growing normally. As this child may have already been undergoing a natural remission, no conclusion can be drawn about the effect of the treatment in this case, except that it evidently had no adverse effect.

COMMENT

In patients with alopecia universalis A.C.T.H. apparently stimulates the germinal epithelium of the diseased hair follicles, with a resultant hair growth which is sustained only while A.C.T.H. dosage is maintained at a high level.

Though these results have been encouraging, in that we have been able to grow hair consistently, they have been discouraging in that no permanent benefit was obtained. They indicate the need for investigating the following possibilities:

(1) That A.C.T.H. permits regrowth of hair owing to its effect on the inflammatory exudate round the hair follicles.

(2) That this phenomenon is due to inhibition of an allergen antibody response by A.C.T.H.

(3) That A.C.T.H. simply increases the blood-supply to the affected hair follicles.

(4) That some hormone is elaborated by the adrenal cortex in man which has a specific stimulating effect on the pilary system.

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Reviews of Books

Supplement to the British Pharmaceutical Codex

Chairman of Codex Revision Committee: C. W. Maplethorpe, ph.c., f.r.i.c. London: Pharmaceutical Press. 1952. Pp. 148. 25*s*.

The appearance of the 1951 addendum to the *British Pharmacopœia, 1948*, entailed issuing a supplement to the *B.P.C.*; and here it is, with numerous amendments and a number of new monographs. These include drugs, such as a ethinylœstradiol and chloramphenicol, which have been added to the *B.P.*, and a number of others whose value has lately become apparent, such as amidone hydrochloride. Aureomycin is now included. A number of new preparations used in treating tropical diseases are incorporated. These include diethylcarbamazine acid citrate, used in filarial infections, and sulphones (dapsone and solapsone), used in leprosy. As usual the brief practical notes provide a reasonably up-to-date evaluation of the drugs concerned, and in the case of antibiotics this information is remarkably full. Readers who do not keep an eye open for new approved names will be interested to find that cyanocobalamin (vitamin B_{12}), troxidone ('Tridione'), and others are now included. Whether, of course, the profession will be in any haste to adopt a name like cyanocobalamin is another matter. Unfortunately the desirability of selecting names that indicate the composition of drugs is occasionally allowed to overshadow the need for a name that will be generally used.

Practical Electron Microscopy

V. E. Cosslett, m.a., m.sc., ph.d., university lecturer in physics, Cavendish Laboratory, Cambridge. London: Butterworth. 1951. Pp. 300. 35*s*.

Electron Microscopic Histology of the Heart

Bruno Kisch, m.d., research associate in cardiology, Mt. Sinai Hospital, New York City. New York: Brooklyn Medical Press. 1951. Pp. 106. $5.50.

The first of these two books grew out of the summer schools in electron microscopy which were held in Cambridge in 1948 and 1949. It is designed to bridge the gap between specialist monographs which describe in detail the construction and theory of electron microscopes, and books which concentrate on techniques for preparing specimens. In Dr. Cosslett's own words: "It is hoped that it will arm anyone who has charge of an electron microscope with adequate knowledge to understand its behaviour and misbehaviour, to embark on the preparation of the main types of specimens, and to delve further on his own account into the published literature." In this aim he has succeeded admirably. He gives a well-written account of the construction of the various electron microscopes that can be purchased, together with sufficient theory of electron optics and of the behaviour of electrons in lenses and in specimens for the user to understand something of what he is doing, and to avoid most of the many pitfalls which beset him.

The first seven chapters deal with theoretical matters, together with instructions for adjusting and aligning the microscope; special requirements for recording electron images photographically are also discussed. Two further chapters provide an excellent introduction to the various methods of mounting specimens, forming thin plastic replicas of surfaces, and "shadowing" specimens with a film of metal a few thousandths of a micron thick so that the detail will stand out. The book ends with a description of the present limitations of electron microscopy and possible future developments.

The book is well printed and contains an excellent set of photographs from centres all over the world. One possible criticism is that there is no coherent discussion of the difficulties of interpreting electron micrograms. Here and there warnings are given that certain physical phenomena may give rise to pictorial artefacts; but for the beginner—and even for the more experienced—a special section dealing with such difficulties would be extremely valuable. This, however, is simply a suggestion for the future editions that are certain to be required. The book can be wholeheartedly recommended both to those who are entering the field for the first time and to those who have been in from the beginning.

The second book is less successful. Of the sixty or so electron micrograms of sections of heart-muscle some are good but all are practically uninterpretable even by Dr. Kisch. In order to assess the present state of "electron microscopic histology" of the heart, it would have been far better to discuss critically the technique of specimen preparation, the limits of correlation between light and electron-microscope results, and the relations between the known physiological and the chemical aspects of muscle. This work may leave the reader convinced that many electron microscopists are still inserting specimens into their microscopes to see what they look like, and are making only half-hearted attempts to interpret the results.

Human Blood Groups and Inheritance

SYLVIA D. LAWLER, Galton Laboratory, University College, London; L. J. LAWLER, senior biology master, William Ellis School. London: Heinemann. 1952. Pp. 85. 3*s.* 6*d.*

THE nine well-established and independent sets of inherited blood antigens have great significance in anthropology, hæmatology, and genetics; and they also have a large potential value in forensic medicine. This brief and up-to-date account of the subject, though intended primarily for the biology student and the layman, could be very useful to medical readers. At the same time the attempt to simplify the subject may not be completely successful. A glossary is provided, but this includes no definition of such words as isotonic, precipitin, globulin, segregation, and diploid. There are also numerous inaccuracies, usually regarding points not directly concerned with the main topic; and the descriptions of Spencer Wells forceps, of syndactyly, and of mutation need to be revised. These errors do not, however, detract seriously from the merits of the book, which include, besides its readable presentation, its convenient size for the pocket.

Problems of Aging

Transactions of the 13th Conference. Editor: NATHAN W. SHOCK. Packanack Lake, N.J.: Josiah Macy, Jr., Foundation. 1951. Pp. 194. $4.

So far as experiment is concerned, the study of age processes is in its infancy. This volume shows that the American public and their government are becoming increasingly aware of the importance of research in this field.

The Federal Security Agency has already established a committee on ageing and geriatrics, and its first venture in sponsoring a general research conference last June drew an audience of 800 biologists. The Adult Education Association of the United States has also undertaken to include the question of ageing, presumably in its broad sociological aspects, in the agenda of its annual conferences. The States of Michigan and Illinois have set up State commissions for study of the question, and other local authorities are expected to follow suit. The growth of public interest extends also to lay social and religious bodies, which are already contributing financial and moral support to research, both in social adjustment for the elderly and in biological and medical research.

At the same conference papers were presented on the endocrine and cardiovascular aspects of age changes, and on the ageing of skin. Gerontologists everywhere will look with interest to the more ambitious meeting to be hel year. For research-workers, more set disquisitions bibliographies would have been useful, but where littl known of a subject the earliest organised discussions m always be in the nature of research colloquia, and these h their own very real value.

With the growth, since the publication of Cowdr standard work, not so much of new fact as of new attitu we may hope for an international symposium cover all aspects of ageing, which the director of resea can use to interest would-be investigators, and t physician to convince administrative bodies of t importance of age studies to our society.

Directory and Catalogue of Collections of Micr organisms maintained in Canada

National Research Council, Ottawa. N.R.C. no. 2

THIS directory gives the addresses of 69 laborato in Canada from which cultures of micro-organisms c be obtained by bona-fide research-workers. Secti headed bacteria, phages, viruses, yeasts, and fungi g some details of the strains kept by the different labo tories, and an index of genera at the end of the bo makes it easier to find a particular species in ot sections. Several organisms of medical interest not ke in culture collections in the United Kingdom may obtained from Canada; these include the Vi typ phages for the typhoid bacillus, phages active agai certain saprophytic acid-fast bacilli, and two of t rickettsias of typhus fever.

The volume, produced by a multigraph process, is loose-leaf form so that new lists may be added and lists brought up to date; it is not for sale. It is to hoped that the organisation controlling the Brit Commonwealth Collections of Micro-organisms will able to arrange publication of later editions as a document obtainable, like the other directories in series, from H.M. Stationery Office. The Canad directory can be seen in the national libraries and some university departmental libraries.

The Drinker (London: Putnam. 1951. Pp. 282. 12*s.* 6*d.*) This book by Hans Fallada, the author of *Little Man W Now ?*, is a near masterpiece on a morbid theme: the unre ting downward course of a man, not devoid of goodness, w takes to drink in order to escape from realities which lacks the resolution to alter. The book was written in c while Fallada was in prison on a charge of attempted mur from which he was subsequently acquitted, and it was n until after his death that the manuscript was found a deciphered. From the first page the reader is gripped a feels himself being sucked down with the autobiographi "hero" into a dark vortex of depravity and misery, lit o by the *ignis fatuus* of illusory hopes or grandiose fantas From a clinical standpoint the observation of what t psycho-analyst would term an orally fixated infantile charac is pitilessly accurate. The fundamental tragedy of H Fallada's pathetic hero is that he is not content to be a Li Man inhabiting this everyday world.

Diagnosis of the Nervous System (10th ed. Lond Edward Arnold. 1952. Pp. 962. 50*s.*).—Sir James Pur Stewart, in 1948, invited Dr. C. Worster-Drought to collabor with him in the new edition of his textbook, which he carried single-handed through nine editions since its f appearance in 1906. Sir James lived, his collaborator tells in the preface, to approve the almost completed work be his death in 1949. This famous textbook has gained w each revision, and much of it has now been rewritten to co developments since 1945. It is a splendid work for stud —clear, informative, and direct, with plenty of illustratio Some of the photographs, indeed, are beginning to acq a patina of antiquity, and the time has perhaps come introduce some patients in more recent costume, with whisk less reminiscent of the Boer war. Their injuries and disea however, are those we see today, and perhaps after all th classic quality only serves to emphasise the perennial nat of the book and its subject. New generations of students c safely trust its teaching (even though the fifth lumbar a first sacral dermatomes, as shown in fig. 40, and in plat and fig. 39, still do not tally).

THE LANCET

LONDON: SATURDAY, MARCH 29, 1952

The Dentists Bill

To judge by the debate in the House of Lords,[1] e only controversial section of the Dentists Bill the proposal to conduct an experiment in the aining and use of dental ancillary workers. Clause 19 the Bill provides that the General Dental Council hich is to succeed to the powers and functions of he Dental Board, and of the General Medical Council n dental matters) is to arrange for the training and ubsequent employment of a number of ancillaries, hose work will include the extraction and filling f teeth. The experiment will last three years, and it proves successful the council will draft regulations o establish a class of such ancillary workers. Parliamentary control is ensured by the provision that hese draft regulations must be approved by a resolution of each House. Then the ancillaries will be mployed, under the supervision of a registered lentist, in the national or local-authority health ervice in hospitals, in school clinics, and in maternity and child-welfare clinics, but not in general dental practice. As the Earl of ONSLOW said, in replying to the debate, the House had divided itself "into two camps: those who more or less agree with the Bill as a whole and those who are worried . . . by the part dealing with the dental ancillary."

In the debate the main argument for this provision was concerned with the disastrous condition of the school dental service, which had only some 700 whole-time officers; 2800 was regarded as the minimum for a reasonably adequate dental service for children and nursing and expectant mothers. This estimate of 2800 is almost certainly too low, since it assumes that one dental surgeon can care for about 2000 children; whereas it is unlikely that a dentist could deal with many more than 1200, until the ravages resulting from lack of treatment in recent years have been made good. There seems, however, to be no prospect of even 2800 dentists being recruited to the school service within the foreseeable future. It is surely unrealistic to expect that the demand of adults for treatment under the National Health Service will be greatly reduced by the proposed charges, and to assume that many more dentists will be led to seek appointment in the school service. We cannot reasonably expect that the service will be rapidly expanded fourfold simply as a result of these charges. It is equally clear, from statistics quoted during the debate, that the shortage of dentists cannot be overcome by rapid expansion in the size of the profession. At present the number of practising dentists is about 10,000; and this figure is being maintained, but not increased, by an intake into the dental schools of about 600 new students each year. The resources for training are being used to the full, and the schools have no vacant places; so any increase in the number of entrants would involve extension of school buildings and expansion of teaching staffs. In 1946 the Interdepartmental Committee on Dentistry,[2] under the chairmanship of Lord TEVIOT, estimated that the number of dentists required was 20,000—a figure that would be reached in twenty years if the annual entry into the schools could be raised to 900. Even if, despite our economic difficulties, the necessary building programme were to be authorised, it is difficult to imagine that the number of suitable candidates could be increased by 50%. The dental schools already have difficulty in filling all their vacant places with students able to follow the course of training and to qualify in the prescribed period. An increase by half in the number admitted could only be achieved by easing the conditions of entry; and similarly the curriculum would have to be simplified. Some who oppose the idea of supplementing the profession by ancillary workers have already suggested that the training course should be reduced by at least one year, so that the number of dentists could quickly be increased. Such a proposal will hardly commend itself to a profession concerned to maintain its status; for it represents a far greater danger to the profession's standing than the establishment of a group of ancillaries to perform defined routine tasks under the supervision of a dental surgeon. The admission to full professional standing and privileges of an ever-growing number of dentists who had qualified after an abbreviated course of training would amount to real "dilution" of the profession; yet fear of such dilution has caused many dentists to oppose the Bill.

Such opponents point out that the dental nurse in New Zealand retires from the service, to marry or for some other reason, after only about ten years' work, whereas the dental surgeon can be counted on to give at least forty years' service. Thus, it is argued, though the cost of training a dentist is at least twice, and his salary as much as three or four times, that of the dental nurse, it would be much more economical, in the long run, for the community to concentrate on expanding the profession than to train ancillary workers. This argument loses much of its force if such an expansion can be attained only at the cost of a serious decline in standards of training. It is, in any case, an argument that applies equally to women dentists, though it has not been suggested that, because she may give up practising when she marries, a woman should be barred from the dental course. In fact, the proportion of women students has steadily risen, and would inevitably rise even more steeply should the annual intake into the dental schools be further increased in an effort to expand the profession. Many local-authority dental services have come to rely on women dentists, who often take full-time appointments until they marry, after which some of them continue to work part-time. It is not unreasonable to expect an equally high proportion of dental nurses to continue their work in the same way. From Lord WOOLTON's presentation of the Bill in the House of Lords it is clear that the Government is aware of this aspect. There is nothing in the Bill to prevent the recruitment of men, as well as women, to the ancillary service; and many young men would be attracted to it if they knew that ancillaries who showed the necessary aptitude would be encouraged to continue their studies and qualify as dental surgeons.

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[1] See *Lancet*, Feb. 16, 1952, p. 363.

[2] Cmd. 6727. H.M. Stationery Office, 1946. See *Lancet*, 1946, i, 206.

The dental ancillary would, however, be no more a partly trained dentist than the nurse is a partly trained doctor. The ancillary would be fully trained in a limited field of dentistry, but would not have the wider professional background gained by the dental surgeon, and would therefore work only under the supervision of a qualified dentist. The medical profession has had no reason to regret its welcome to ancillaries, such as nurses, physiotherapists, chiropodists, and dietitians, who perform an increasing number of routine tasks. Many of the functions of these ancillary medical workers demand great skill, and a life may depend upon their being correctly performed; yet it is not proposed that they should be carried out exclusively by doctors. The dental profession cannot hope to meet all the demands on it, and its members would be showing imagination worthy of their status by admitting in principle the necessity for ancillary workers, and using their experience to devise the best method, in the public interest, of organising and supervising their work. Lady MELLANBY, whose opinions are greatly respected in the profession, has said of the New Zealand scheme:

> "I have never seen so many five-year-old children with such beautifully filled teeth. I am afraid I must admit that I have been horrified at the state of some of the children's mouths I have been examining in London since my return. Give me dental nurses of the type used in New Zealand every time for young children."

Hæmochromatosis

HÆMOCHROMATOSIS, though uncommon, presents such a curious clinical and pathological picture that it has aroused great interest. Seventeen years ago SHELDON[1] described the diagnostic tetrad of skin pigmentation, cirrhosis of the liver, diabetes mellitus, and hypofunction of endocrine glands; the patients were predominantly male. Pathologically the diagnostic feature is deposition of iron in the form of hæmosiderin in the liver, heart, and all glandular tissue, including the glands of the stomach, the salivary glands, and the sweat glands in the skin; in addition there are deposits of hæmofuscin, an iron-free pigment derived from melanin. At necropsy the total iron in the tissues of these patients has been estimated at 20–50 g., compared with the normal maximum of 5 g. It is generally thought that the deposits of iron in the liver and pancreas stimulate the proliferation of fibrous tissue, which, in turn, slowly causes failure of these organs. SHELDON found that hepatic cirrhosis was present in all cases; in 93% this was of the hypertrophic type, and in only 7% was it atrophic Diabetes mellitus was present in 78% of the patients Pigmentation was present in at least 80%, and th curious mixture of leaden-grey and bronze shades was very characteristic. Other common clinica features are premature thinning of the hair, and impotence together with testicular atrophy. By th time the patients come for treatment the disease is usually far advanced, and it is only a matter of tim before liver failure proves fatal.

How or why iron pigment is deposited in this way has been a mystery. Possibly, however, recent work in the field of nutrition may provide a clue. GILLMAN and GILLMAN[2] found increased absorption and storage of iron in South African Negroes who live on a staple diet of maize; and WALKER and ARVIDSSON[3] pointed out that the iron came from the iron pots in which the maize meal porridge was cooked, 100–150 mg. o iron being ingested daily; in some of these people liver lesions developed which were similar to those in hæmochromatosis. Then HEGSTED et al.[4] showed that in rats the absorption and storage of iron can be much increased if the phosphate in the diet is grossly diminished. It hardly seemed likely, however that gross dietary deficiencies played much part in classical hæmochromatosis; and a survey by ALTHAUSEN et al.[5] in Australia has confirmed this. They compared the dietary histories of 16 patients with typical hæmochromatosis with those of a contro group with similar social and occupational background; and they found no notable difference and no evidence of severe deficiencies. The Australian workers carried out a series of investigations in 1 of their cases. Of an extensive range of liver function tests the hippuric-acid synthesis and the bromsulphalein-retention tests proved the most useful, and these gave abnormal results in most cases. Liver biopsy in 14 patients showed cirrhosis and hæmosiderin deposition in 11; in the other 3 hæmosiderin deposits were present but cirrhosis had not yet developed. Of 23 cases, 18 had diabetes mellitus; this was easily controlled in all except 1. The other pancreatic functions were investigated without really clear-cut results. They also carried out biopsies of skin, and of stomach mucosa by the method of WOOD et al.[6] The skin showed increased melanin in the epidermis; the deposition of hæmosiderin was variable, but it concentrated especially in the sweat glands. Gastric biopsy showed hæmosiderin in the chief cells of the glands in each of 11 cases, and in 9 of these the gastric secretion of acid and pepsin was unimpaired. ALTHAUSEN and his co-workers also estimated the serum-iron in 18 patients and found that in 12 the level exceeded the upper limit of normal; in 5 patients serum-iron levels were definitely higher after an interval of fifteen months. This finding fits in with observations made with radioactive iron tracer. DUBACH et al.[7] noted that a patient with hæmochromatosis who had no anæmia nevertheless retained 20% of a test dose of radioactive iron, and

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1. Sheldon, J. H. Hæmochromatosis. London, 1935.
2. Gillman, J., Gillman, T. *Gastroenterology*, 1947, 8, 19.
3. Walker, A. R. P., Arvidsson, U. B. *Nature, Lond.* 1950, 166, 438.
4. Hegsted, D., Finch, C. A., Kinney, T. D. *J. exp. Med.* 1949, 90, 147.
5. Althausen, T. L., Doig, R. K., Weiden, S., Motteram, R., Turner, C. N., Moore, A. *Arch. intern. Med.* 1951, 88, 553.
6. Wood, I. J., Doig, R. K., Motteram, R., Hughes, A. *Lancet*, 1949, i, 18.
7. Dubach, R., Callender, S. T., Moore, C. V. *Blood*, 1948, 3, 526.

only 2% appeared in the blood; they calculated that the patient had absorbed five times as much iron as he could build into hæmoglobin. **Alper** et al.[8] in South Africa showed that a non-anæmic patient with hæmochromatosis absorbed and retained at least five times as much iron as the controls, and that as much as 60% of a test dose was retained. Five months later at least 15% of the test dose was still in the liver, and some was retained in the heart. This patient died at the early age of 21, and necropsy showed typical changes already well developed in the organs. **Balfour** and others[9] found that in a more chronic case the rate of iron uptake after a test dose was much less startling.

It seems clear that an important factor in the pathogenesis of hæmochromatosis is excessive absorption of iron from the alimentary tract; the mechanism that in the normal non-anæmic person limits the absorption of iron to very small amounts is not working properly, and since absorbed iron is excreted only very slowly deposition in the body tissues inevitably follows. If excessive iron absorption is the important factor in hæmochromatosis, it might be rational to reduce the iron in the diet as far as possible. Unfortunately by the time patients come for treatment the damage is done. **Davis** and **Arrowsmith**[10] did try the effect of repeated venesection in 3 patients with hæmochromatosis, and they claimed that serial liver biopsies showed lessening of the hæmosiderin and improvement in the cirrhosis. Incidentally in these cases the red cells regenerated very quickly, and this suggests that the hæmosiderin iron may be utilisable for hæmoglobin formation. The cause of the excessive absorption of iron is not yet known. The process must be slow, since 20–50 g. of iron is found in the body of patients after death, whereas iron in the diet rarely exceeds 20 mg. daily and only a proportion of this will be absorbed; and **Althausen**'s results show that iron deposition can be advanced before cirrhosis of the liver appears.

The new facts do not disturb the idea that classical hæmochromatosis is the end-result of an inborn error of metabolism; and now that the site of the error has been defined further research may enable us to determine its nature and perhaps start preventive measures in time.

Research on Mental Health

"How should research be furthered?" is a question that Œdipus would have found it a good deal harder to answer than the childish riddle set him. If the Sphinx had further restricted the question to research in psychiatry (with one aspect of which Œdipus's name was later to be closely connected) his difficulty would have been greater still; for the wind of research tends to blow where it listeth, and it has not yet blown to much purpose in clearing up the major problems of causation, pathogenesis, and prevention in mental disorder.

The importance of these problems is now fully recognised. Several American organisations, including the Rockefeller Foundation and the Commonwealth Fund, have done much to advance research and training in this branch of medicine, and so, in this country, has the Nuffield Foundation; the Beit trustees have likewise sought to help by expressing a preference for research into mental disorder. The newly formed Mental Health Research Fund, eager to advance the same cause, took the wise preliminary step of holding a conference at which those most intimately engaged in the work could tell each other, and the laymen who are alive to the importance of the matter, what steps would be most likely to bring us nearer the goal. As the guests of Magdalen College, Oxford, the members of the conference were under an obligation to its founder, **William of Waynflete**, whose particular wish it was that no-one should engage in sophistry; and, happily, no sophistry marred their deliberations. At this conference, which we report on another page, it was sufficiently plain that valuable research is going on, and that its nature and rate of progress are chiefly determined by developments in the supporting sciences. The methods and concepts that emerge in anatomy, biochemistry, physiology, psychology, and the biological and social sciences generally, are those on which the investigator in mental health must depend. It is therefore a nice question, which the conference did not succeed in answering, whether progress is aided more by assisting first-rate study in neuro-anatomy, neurophysiology, psychology, genetics, and sociology, which have at present no obvious and direct bearing on mental disorder, or by inquiries which apply unequivocally to psychiatry. Naturally most of the speakers dealt with the latter, but such studies as those of which Prof. W. E. **Le Gros Clark**, F.R.S., Prof. **Roger Russell**, and Dr. G. W. **Harris** spoke testified to the impetus given to psychiatry when researches not primarily oriented towards mental disorder advance our knowledge of neural function and structure or of psychology. The conference gave recognition to this in its recurring emphasis upon research into the normal—a synonym for what is studied in all university departments concerned with the biological sciences.

The members of the conference would have been more than human—as patients sometimes imagine psychiatrists to be—if they had not availed themselves of the occasion to declare their practical difficulties in getting material, recruits, and facilities for their work, and in keeping abreast of what is going on elsewhere. Naturally also they fell in with current trends towards team-work, emphasising the need for a "multi-disciplined" approach. It was, however, pointed out by Sir **Geoffrey Vickers**, to whom many of the issues presented at the conference, especially in respect of training, were familiar in other professional fields, that there may be dangers in persuading people to engage in joint or "integrated" inquiries when their interests and capacity lead them to concentrate on a narrow subject perhaps remote from the problem of mental health. In the long run it is from a few people with the requisite gifts and interests that advances through research chiefly derive. Research funds must look to them for the fruitful ideas and achievements that will enable the general run of investigators to get over obstacles which have proved so redoubtable in mental disorder.

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[8] Alper, T., Savage, D. U., Bothwell, T. H. *J. Lab. clin. Med.* 1951, 37, 665.

[9] Balfour, W. M., Hahn, P. F., Bale, W. F., Pommerenke, W. T., Whipple, G. H. *J. exp. Med.* 1942, 76, 15.

[10] Davis, W. D. jun., Arrowsmith, W. R. *J. Lab. clin. Med.* 1950, 36, 814.

Annotations

THE AWARD

THE patience and perseverance of the General Medical Services Committee in its effort to secure proper remuneration for general practitioners is now rewarded; and on another page we print the result of the adjudication by Mr. Justice Danckwerts. His decision, based, not upon the number of patients served, but upon the number of doctors in the service, means that for the year 1950–51 the sum due to the Central Pool is £51,252,000 instead of the £41,533,000 already paid; and the total extra amount involved from the start of the service in 1948 to the end of the financial year 1952–53 is likely to be about £40 million. It now remains for the Working Party set up by the Ministry of Health and the General Medical Services Committee to determine how the money should be distributed; and finally Parliament will be asked to approve the allocation of these extra millions. We are thus in sight of the end of a dispute which has continued for nearly four years—namely, how the Spens Report, which was the agreed basis of remuneration, should be interpreted.

The last Government—or the Treasury—by their continued reluctance to adopt a proper betterment factor, have allowed the sums overdue to mount high; and the present Government will need to remind other groups in the population, who have just been asked to pull in their belts once more, that the adjudication affords, not a rise in pay, but a settlement of back pay and a yardstick for the future. Though satisfactory for individual practitioners, this settlement may prove no less satisfactory to the health service. In the first place, it may help to rescue general practice—a partly depressed area—from its despondency, by encouraging more young doctors to compete for admission to it. Secondly, if the Working Party settles effectively its task of allocating the money, entry into practice will be eased, and the temptation to accrue over-large practices will be removed. These would be no mean gains to medicine and the public.

INTERNATIONAL HEALTH

THE expanding scope and increasing complexity of modern medicine make it ever more difficult, yet at the same time more necessary, to understand what is being done by other members of our profession. The appearance of the first textbook on International Health Organisations[1] is therefore an event. The author, Dr. Neville Goodman, has in various capacities served the Office International d'Hygiène publique, the League of Nations, Unrra, and the World Health Organisation, and writes with the authority of this long experience. His book sets out clearly the aims and achievements of these bodies and their predecessors, starting with the first international conference on infectious diseases, held in Paris in 1851. Descriptions of methods of procedure and the composition of organisations form the basic anatomy of the subject, and the essential bones are elegantly described. The accounts of functional activities are brought to life by a pretty wit and many shrewd observations of the individuals who compose the organisations, while 52 illustrations strike a nice balance between committees in world capitals and field work in remote places. An account is also given of the relation to health problems of other United Nations organisations, notably Unicef, F.A.O., Unesco, and I.L.O., and there is a chapter devoted to the international health work of the Society of Friends (Quakers), the Red Cross, and the Rockefeller Foundation. The curious will also find a factual and documented account of how the countries now behind the Iron Curtain at first coöperated with and then withdrew from W.H.O.

Very properly Dr. Goodman begins with a chapter for sceptics entitled *Why "International" Health?* Six solid achievements are described—the control of cholera during the Mecca pilgrimages, the control of the spread of rats and plague by ships on international voyages, the biological standardisation of therapeutic substances, the treatment of venereal disease among seamen, the medical relief of "displaced persons," and the eradication of malaria in Sardinia. These are all definite accomplishments, and, except for the last, would have been impossible without real international coöperation. The final chapter deals with future problems. There are nine great human scourges which, by using existing knowledge, we could now reduce to minor proportions—namely, louse-borne typhus, malaria, cholera, smallpox, yellow fever, syphilis, tuberculosis, enteric fever, and diphtheria. Against each of these great "local" victories have been scored, and W.H.O. is at present undertaking campaigns on a gradually widening front. But "total" victories cannot be obtained unless the nations work together.

All this is a long way from 1851 and the first international conference on infectious diseases at Paris. The delegates there were concerned chiefly with cholera, and they represented people who were afraid. There was a double fear: cholera might kill and cholera might also diminish trade. It was a threat both to life and economic security throughout the world. But the delegates also represented people with wide sympathies, who wished to stamp out an ugly disease and so reduce the sum of human misery. This mixture of motives, noble and less noble, has been behind all international health organisations and still persists. Today we wish to study war for much the same motives that a hundred years ago our grandfathers and great-grandfathers studied cholera; and it is right and necessary to do so. At the same time we should not forget that some of the old problems remain. That we are in a position to defeat a disease does not mean that it is actually defeated; and the forces on our side are not so great that we do not need to unite them.

CEREBRAL SYMPTOMS IN CARDIAC INFARCTION

USUALLY the first and foremost symptom of cardiac infarction is pain; but occasionally this is slight or absent, or is rapidly superseded by other symptoms. Notable among these are unconsciousness, convulsions, hemiplegia, or other evidence of local brain injury. Severe pain can itself cause syncope, and it is more likely to do so when the blood-pressure is also low, as a direct cardiac effect. In a large series of cases of cardiac infarction in American Servicemen under 40 years of age, Yater et al.[1] noted unconsciousness in 11%, and convulsions in 4%; and all the patients with convulsions died. In the elderly, cardiac infarction may manifest itself in transient or long-continued unconsciousness and hemiplegia, and the true diagnosis may then be revealed only by necropsy.[2 3] In five such cases described by Cole and Sugarman[2] necropsy brought to light no evidence of a cerebral vascular lesion, and these workers suggest that the neurological disturbance may have been due to ischæmia and anoxia from fall in blood-pressure, associated with narrowing of the cerebral arteries. Syncope and convulsions may be caused by slow heart-rate due to heart-block or even extreme sinus bradycardia, and also by auricular fibrillation and flutter and the ventricular and auricular tachycardias. Primary ectopic tachycardia

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1. International Health Organisations and Their Work. By N. M. GOODMAN, M.D., F.R.C.P. With a foreword by Sir Wilson Jameson. London: J. & A. Churchill. 1952. Pp. 327. 35s.

1. Yater, W. M., et al. *Amer. Heart J.* 1948, 36, 481.
2. Cole, S. L., Sugarman, J. N. *Amer. J. med. Sci.* 1952, 223, 35.
3. Bean, W. B., Read, C. T. *Amer. Heart J.* 1942, 23, 362.

(which may cause cardiac pain and subsequent inversion of the T wave) has to be distinguished from an abnormal rhythm complicating infarction. Similarly chest pain and syncope due to aortic stenosis may be thought to indicate coronary thrombosis, especially as deep inversion of the T wave is usual; but this mistake can be avoided by recognising the clinical signs of the valve lesion, and by the pattern of the T wave and S–T segment which differs from that myocardial ischæmia.

Cerebral symptoms starting days or weeks after cardiac infarction may be due to an embolus from the left ventricle or to arterial disease of the brain. The heart-attack itself may cause relatively little pain, for which the patient does not seek medical advice. In such a case, when the patient is first seen by the doctor with, say, hemiplegia, the original heart condition may easily be overlooked unless the doctor is on his guard.

DOUBLE INFLUENZA

By isolating both A and B influenza viruses from a patient who had two attacks of influenza within 13 days, Burnet and his colleagues[1] provided one explanation of a well-known clinical observation. There is ample serological evidence that these viruses hunt in couples, or at any rate do not respect one another's preserves, but though the two types are often active even in relatively small epidemics, one serological strain of one type usually predominates over other strains in a ratio of at least 3 : 1. At the Rockefeller Institute Kilbourne and his associates[2] now describe an outbreak in which there were about two cases caused by influenza A to each case caused by influenza B, and nearly a quarter of the patients were infected with both viruses at the same time. The outbreak occurred among children in an institution who had few contacts with the outside world, so it was convenient for investigation. Of the 115 children studied, 37 had definite influenzal symptoms and three strains of A virus and two strains of B were isolated from these. All but 4 of the 37 ill children gave positive serological tests against one or both types of influenza virus, but 10 symptomless children (8% of the total tested) also developed antibodies, in one case to both viruses. Infection with A virus was proved serologically in 25 children, with B virus in 11, and with A and B in 10, while 60% of the children had negative tests. In the children who had clinical influenza the mean antibody titres increased 32-fold, whereas, as would be expected, those who escaped had the highest initial titres of immune bodies. The most interesting group were the children who had only one clinical illness but showed serological evidence of a double infection with the two viruses within a maximum period of a month. It is known that chick-embryos and mice can be infected with A and B viruses simultaneously, but little is known about the antigenic response of mammals doubly infected with viruses which are capable of reciprocal interference. By infecting hamsters with the freshly isolated A and B viruses, separately and combined, and then measuring their antibody levels, the occurrence of double infections was established beyond question, but there was partial interference since the antibody titres were lower in the doubly infected hamsters than in those infected with only one virus. There is therefore experimental support for the double infections in children demonstrated by the Rockefeller workers and by Francis et al.[3] in the spring of 1947. Having learnt to expect, if not to predict, the numerous manifestations of the genetic lability of influenza A virus, we must now be prepared to find two or even three distinct influenza viruses sharing the same human host at one time.

ECONOMICAL PRESCRIBING

The first issue of the periodical bulletin on the cost of prescribing, which the Minister of Health mentioned in a speech on March 14,[1] has been going out to general practitioners this week. The aim of *Prescribers' Notes* is to cut the rising drug bill of the National Health Service by showing doctors how to give exactly what they want in the cheapest way. At the same time the practical information it provides will enable them to save time as well as money in prescribing. What it will *not* do, its Editor explains, is to restrict or interfere with their choice of treatment.

The first notes come in a small loose-leaf binder to which further issues may be added as they appear. They are very short—only ten pages—and the busy practitioner need spend no more than a few minutes reading them. He can then keep them conveniently to hand for reference, so that should the need arise, he can see at a glance, for example, the various sizes of surgical dressings, or the relatively few types of infection in which chloramphenicol is known to be better than sulphonamides or penicillin. He is reminded how much cheaper cellulose tissue is than cotton-wool, and of the cost of chloramphenicol at current prices. The first issue also gives statistics showing the sharp rise in the number and cost of prescriptions since 1948 and the increasing proportion of proprietary drugs dispensed.

The editorial committee have done well. Brief and helpful advice of this kind will surely be welcome. It comes not from those primarily concerned with £ *s. d.*, but from a committee which includes several experienced and active practitioners who appreciate the doctors' sensibilities and who know what can be done to economise without reducing the standard of treatment.

TYPES OF DIABETES MELLITUS

Young diabetics usually depend on administered insulin to prevent ketosis, and are therefore thought to have a primary insulin deficiency, although the fact that they commonly require more insulin than do pancreatectomised patients[2] suggests that insulin lack may not be the only factor disturbing their carbohydrate metabolism. In contrast diabetes coming on later in life, particularly in the obese, seldom calls for injections of insulin. Here the mechanism is presumably either an excessive demand outstripping the intrinsic insulin supply, or perhaps the presence of some factor opposing its action. The work of Bornstein and Lawrence[3] on plasma-insulin supports these familiar hypotheses, and suggests that it may be possible sharply to divide diabetics into two categories—those with, and those without, any intrinsic supply of insulin. The fact that those with insulin are of the older age-group would seem to preclude transition from the group with to the group without insulin; yet recent reports tend to undermine this superficially secure reasoning. Zubrod and colleagues[4] have made a detailed study of the type of diabetes associated with the nodular intercapillary glomerulosclerosis of Kimmelstiel and Wilson.[5] At necropsy on 190 diabetics Zubrod and his associates distinguished three groups on the basis of the renal lesions: (1) those with Kimmelstiel-Wilson lesions, (2) those with other types of renal lesion, and (3) those with no renal disease. Clinically the Kimmelstiel-Wilson group had differed from the other two in requiring progressively less insulin although initially needing fully as much, and also in displaying virtually no tendency to ketosis. On the basis of these findings insulin was withdrawn from six patients who were thought to have

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1. Burnet, F. M., Stone, J. D., Anderson, S. G. *Lancet*, 1946, i, 807.
2. Kilbourne, E. D., Anderson, H. C., Horsfall, F. L. *J. Immunol.* 1951, 67, 547.
3. Francis, T., Quilligan, J. J., Minuse, E. *Science*, 1950, 112, 495.

1. *Lancet*, March 22, 1952, p. 622.
2. Goldner, M. G., Clark, D. E. *J. clin. Endocrinol.* 1944, 4, 194.
3. Bornstein, J., Lawrence, R. D. *Brit. med. J.* 1951, i, 732.
4. Zubrod, C. G., Eversole, S. L., Dana, G. W. *New Engl. J. Med.* 1951, 245, 518.
5. Kimmelstiel, P., Wilson, C

Kimmelstiel-Wilson lesions.[6] One of these was previously inadequately controlled on 50–130 units a day; yet he showed no ketonuria during thirty days without insulin, despite the presence of an abscess and fever. Even on a high fat diet for four days there was still no ketonuria or change in the carbon dioxide combining-power of the blood. Again in the other five cases, which were milder, ketonuria did not develop when insulin was withheld. The diabetes associated with Kimmelstiel-Wilson lesions seems to behave, therefore, as if there is not a complete lack of intrinsic insulin, although at the start it may be of the insulin-deficient type.

Until we have reports of plasma-insulin assays in such patients we are left to wonder whether perhaps they are producing excessive quantities of glycogenolytic factor from the pancreatic α cells, which have also been credited with ketosis-preventing properties,[7] or whether by an increased turnover rate of the Krebs tricarboxylic-acid cycle they dispose of the intermediates of fat metabolism [8] with unusual efficiency.

DRUG ADDICTION IN ADOLESCENTS

A LOT of publicity has been given in recent months to the prevalence in large American cities, especially New York, of addiction to such drugs as marihuana and heroin among what are nowadays known as "teen-agers."[9] Prof. A. R. Lindesmith,[10] of Indiana University, suggests that the relatively high incidence of drug addiction in the U.S.A. is due to the police policy of prohibition, which drives it underground so that it becomes a rich source of revenue for racketeers. The addict is thus brought into contact with the criminal underworld by craving for his drug; moreover, to earn enough to pay for it, he will himself take to peddling drugs and try to spread the habit among his acquaintances, or embark on other criminal ways of making money. The U.S.A. is supposed to have at least 48,000, and more probably 100,000, addicts; and Mayor Impelliteri's committee of inquiry estimated that there were 45,000–90,000 in New York City alone; in the first nine months of 1951, 2837 narcotics cases were entered in that city's police records. F.B.I. figures for the first half of 1951 show that almost half the narcotics offenders were under 25 years old.

Toolan et al.[11] remark on the recent sudden increase in heroin (diacetylmorphine) addiction; from 1941 to 1950 an average of 20 patients was admitted to Bellevue Hospital for heroin or morphine addiction. In people under 21 years of age no such case was detected between 1940 and 1948; in 1949 there was 1 case, and in 1950 11 cases; but in the first seven months of 1951 260 of these youngsters were admitted, their ages ranging from 14 to 20. Of 36 consecutive male admissions described by Toolan *et al.* all but 2 were Negro or Puerto Rican; and all were from Harlem, where young people suffer from discrimination against their racial groups and the rate of crime and disease is higher than anywhere else in New York. Few withdrawal symptoms were found among these adolescents: many experienced no ill effects; some were restless and had increased sweating and lacrimation; about one in five required small doses of amylobarbitone. One serious complication was encountered: 3 youths who had shared the same hypodermic needle developed hepatitis, from which 1 died with acute liver atrophy. The development of the addiction begins with the youngsters being introduced to drugs by their friends or by a pedlar, who gives them drugs free in order to initiate them. According to an account in the *New Yorker* [12] they usually start by smoking marihuana cigarettes ("reefers"); then they are induced to try heroin ("horse"), first by sniffing it (a "snort"), next by subcutaneous injection ("skin-popping"), and finally by direct intravenous injection ("main-lining"). The addict injects himself, using an eye-dropper fitted to a hypodermic needle, which may be shared with others and is seldom sterilised. There is a feeling of anxiety immediately after taking the drug, then euphoria and an increased sense of self-confidence. A feeling of floating through space is often described. The boys lose their aggressive and sexual drives, taking little interest in girls. They may also find it difficult to urinate, for the drug causes spasm of the vesical sphincter.[13] Depression follows the euphoria, and in an attempt to overcome this larger and more frequent doses are taken. When this true addiction has developed boys commonly become delinquent, peddling the drug to friends, truanting and stealing in their attempt to get enough money to keep them in the drug.

Toolan and his co-workers found that these boys, compared with a control group, were non-aggressive and passive, having weak and superficial relationships socially but a close, empathic relationship with their mothers. They live a fantasy life, with grandiose day-dreams, becoming increasingly isolated and withdrawn from social contacts and from the real world, in which they feel inferior and insecure. While "high" they prefer to be alone in a darkened room, listening to the radio and chain-smoking. As a group, these boys are not hoodlums or incorrigible psychopaths but are suffering from character disorders of a neurotic type peculiar to the adolescent who is growing up in a difficult community. Toolan and his associates point out that in adolescence the character structure is not fixed but is in process of adjustment, and that severe psychological disturbances at this age may clear up without psychotherapy. At the same time, heroin addiction with its attendant social withdrawal during the period of adolescent adjustment may have very crippling effects on the personality. They recommend strenuous police action to eradicate the illegal sale of narcotics; educational programmes directed at adolescents and at those responsible for their welfare; the expansion of psychiatric facilities for treatment; and treatment centres for reablement, with trial visits to the home. The severe restrictive legislation recently demanded by the attorney-general, Mr. N. L. Goldstein, includes educative and therapeutic measures, but also the possibility of life-sentence for a third offence against the narcotic laws. The curable addict is to be given compulsory treatment and reablement; the incurable is to be isolated from the public. It is to be hoped that the penal element in these proposals will not drive the narcotics traffic still deeper into the underworld and add to the hopeless sense of isolation of its victims. If the addict has to have his drug—failing a cure—it is surely better for him to get it honestly from his doctor than from the pedlar at the corner of the block.

In the wider sphere of international control the latest report by the Permanent Central Opium Board [14] reveals a disquieting state of affairs. Among the countries which have failed to supply statistics are the main producers of raw materials for drugs of addiction. The government of India, for example, "does not seem to be in a position to ascertain the production, stocks, exports, &c., of raw opium." Neither Peru nor Bolivia—the main producers of coca leaves—has provided statistics; but Peru has made the production of crude cocaine a State monopoly. In Persia 333 tons of raw opium "disappeared" during 1950; and in Italy 164 kg. of diacetylmorphine also isappeared." In that year the declared production diacetylmorphine for the whole world was 453 kg.; l at its meeting last month the W.H.O. Expert Com- ttee on Drugs Liable to Produce Addiction recom- nded that this drug should no longer be used for dical purposes, since it can now be replaced by other rphine derivatives or by new synthetic substances. ogether fifty countries have given notice that they ve discontinued, or are willing to discontinue, the dical use of diacetylmorphine. Clearly, however, thing short of total suppression of manufacture roughout the world will ensure that this drug does not l into addicts' hands; and there is little present hope such unanimous action. Meanwhile in the U.S.A. a ive against drug pedlars is reported[15] to be causing sharp reduction in the number of teen-agers needing mission to hospital.

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[6] Dana, G. W., Eversole, S. L., Zubrod, C. G. *Bull. Johns Hopk. Hosp.* 1952, 90, 98.

[7] Thorogood, E., Zimmerman, B. *Endocrinol.* 1945, 37, 191.

[8] Beatty, C. H., West, E. S. *J. biol. Chem.* 1951, 190, 603.

[9] See annotation, *Lancet*, 1951, i, 1356.

[10] *New York Times*, Dec. 16, 1951.

[11] Toolan, J. M., Zimmering, P., Wortis, S. B. *N.Y. St. J. Med.* 1952, 52, 72.

[12] *New Yorker*, Nov. 10, 1951, p. 44.

[13] Sollmann, T. A Manual of Pharmacology. Philadelphia, 1940.

[14] Permanent Central Opium Board: Report to the Economic and Social Council on Statistics of Narcotics for 1950 and the Work of the Board in 1951. United Nations, Geneva, 1951.

STANDARDISED SENNA

THE anthracene purgatives, of which aloes, rhubarb, scara sagrada, and senna are the most familiar in ngland, owe their activity to the "emodins," a group glycosides of di- or tri-hydroxyanthraquinone, of hich each contains two or three examples. Various ixtures of "emodins" are also used as laxatives, but, often happens in therapeutics, the active principles are the whole less efficient than the crude drugs. In this se the explanation may lie in the relative insolubility the active principles in the intestinal contents. Senna ovides an exception to this general rule, for its glyco- des, sennosides A and B, which were first isolated by Stoll nd colleagues[16] ten years ago, are reliable as laxatives hether they are given by mouth or subcutaneously. hey are absorbed into the blood-stream and re-excreted to the gut, but otherwise their mode of action is still ncertain. Straub and Triendl[17] thought that they stimu- te the nervous mechanism of peristalsis, producing a ood imitation of normal defæcation. Lately Fairbairn and aleh[18] have shown that senna contains a small amount f a third glycoside, another anthracene derivative, hich exerts a synergistic effect on sennosides A and B; y mixing the two sennosides with 14% of the third lycoside their biological activity is increased by two- hirds.

In view of the clinical value and respectable antiquity f senna it is surprising that no method of assay has et been worked out and included in one of the pharma- opœias. While there was no standardised preparation he dosage was bound to be rather haphazard. Fairbairn nd others,[19 20] however, have devised satisfactory hemical and biological methods for the assay of enna, and also of rhubarb[21] and cascara.[22] Fairbairn and Michaels[23] assayed the *B.P.* preparations of senna by these methods and found that the liquid extracts contained less than a tenth and the concentrated infusions less than a sixth of their expected glycosidal content. Some proprietary preparations tested were much more effective than the official ones, though they were still only 30–40% as active as the theoretical maximum. The only preparation which retained the full laxative activity of crude senna was a granular product made from the pod after the inactive seeds have been removed. The remaining pericarp, powdered and standardised, is said[24] to retain its activity for long periods. This is used for preparing the granules. The great advantage of prescribing a standardised preparation of constant laxative action is that, once the dose for each patient is decided, there should be no griping, since this seems to be a symptom of overdosage.

THE BEGINNINGS OF LEPROSY

IN his brief monograph on the histology of early leprosy,[1] profusely and beautifully illustrated, Dr. Khanolkar quotes the words of Anatole France: "There are some that will say . . . this is not the true doctrine. There are others who will say I have said nothing more than what everyone already knows." The passage gives us a glimpse of the mind of a patient worker, who, reviewing the history of a subject, gathers what seems worth retaining from the past, adds his own carefully documented findings, and so produces an outstanding contribution to medical knowledge. He sets out the evidence showing that the leprosy bacillus enters the body through the skin and has a predilection for subcutaneous nerve tissue, particularly early in life when there is a continuous process of degeneration and regeneration, and in areas where the skin is subject to minute injuries and friction. Leprosy is neural in its inception, and *Mycobacterium lepræ* first appears in clinical lesions in the small nerve plexuses in the skin, travelling up the finest nerve twigs in an ascending infection. This carefully reasoned hypothesis is substantiated by Dr. Khanolkar's painstaking studies of sections from early lesions. The silent phase of the disease—before actual clinical symptoms manifest themselves—is lucidly explained and finely illustrated by drawings. Why some lesions become tuberculoid and others lepromatous is logically set forth, showing that a classification of leprosy is practicable and must be based—like the Havana and South American classifications—on the immunology of the disease, due stress being placed on the lepromin test. Dr. Khanolkar shows that the development of leprosy in the body depends on the bacilli being able to burst out from the subcutaneous nerves and nerve plexuses of the skin into the dermis. The subsequent extension of the disease is determined by the response of the tissue to its mycobacterial invader. If the tissue response is weak, lepromatous leprosy ensues: if it is vigorous, the tuberculoid type is likely to develop. Dr. Khanolkar's evidence that the bacilli can remain in the granular form in the nerves should encourage the clinician to be cautious not to discontinue sulphone therapy too soon and so increase the likelihood of relapse.

This monograph may well prove a landmark in leprosy research.

ANTIBIOTICS IN AMŒBIASIS

FOR some years almost every new sulphonamide or antibiotic has been hailed as the drug of choice for treating the acute stage of amœbiasis, but none has proved ideal. It is now recognised that drug treatment should aim at eradicating the secondary bacterial invaders as well as the pathogenic amœbæ themselves.

Several workers have found aureomycin a very active amœbicide. Armstrong et al.[2] report from Durban an immediate-cure-rate with this antibiotic of about 94%; but the relapse-rate is also high, and whether it is preferable to other amœbicides remains undecided.[3] The antibiotic spectrum of aureomycin is similar to that of chloramphenicol; but chloramphenicol is less effective against the disease in man,[4] though in mice it seemed more active than aureomycin as a prophylactic against infection with *Entamœba histolytica.*[5] According to Most and his colleagues[6] terramycin is effective in the treatment of amœbiasis in man. They treated 41 cases with aureomycin, terramycin, or bacitracin. After 2 weeks' treatment terramycin and aureomycin were found to be 100% effective, but bacitracin only 59% effective. The cases treated with terramycin had not relapsed after $2^1/_2$ months whereas with aureomycin the relapse-rate was 40%. Most and his associates felt, however, that if the patients treated with terramycin had been followed up for longer the relapse-rate might have been similar to that with aureomycin. The experiment was so designed that, while it demonstrated the efficacy of terramycin, the superiority of terramycin over aureomycin could not be established. This surprising activity of terramycin was confirmed by giving it for 10 days to 222 patients in an infirmary with an infection-rate of 49%. The infection was virtually eliminated for at least 6 months after treatment. The clinical effectiveness of terramycin has been confirmed by Killough and Magill,[7] who state, however, that it cannot prevent amœbic hepatitis and hepatic abscess. These complications respond to chloroquine; and Killough and Magill suggest that the combined administration of chloroquine and terramycin might prove more effective than either drug alone, for the treatment of both the dysentery and the hepatitis.

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[15] *New York Times*, Feb. 10, 1952.

[16] Stoll, A., Becker, B., Kussmaul, W. *Verh. schweiz. naturf. Ges.* 1941, p. 235.

[17] Straub, W., Triendl, E. *Arch. exp. Path. Pharmak.* 1937, 185, 1.

[18] Fairbairn, J. W., Saleh, M. R. I. *J. Pharm. Pharmacol.* 1951, 3, 918.

[19] Lou, T. C. *Ibid*, 1949, 1, 673.

[20] Fairbairn, J. W., Michaels, I. *Ibid*, 1950, 2, 807.

[21] Fairbairn, J. W., Lou, T. C. *Ibid*, 1951, 3, 93, 225.

[22] Lou, T. C., Fairbairn, J. W. *Ibid*, p. 295.

[23] Fairbairn, J. W., Michaels, I. *Ibid*, 1950, 2, 813.

[24] Ryan, H. A. *Pharm. J.* 1951, 167, 115.

[1] Khanolkar, V. R. Studies in the Histology of Early Lesions in Leprosy. *Spec. Rep. Ser. Indian Coun. med. Res.* no. 19, 1951.

[2] Armstrong, T. G., Wilmot, A. J., Elsdon-Drew, R. *Lancet*, 1950, ii, 10.

[3] Killough, J. H. *Proc. R. Soc. Med.* 1952, 45, 109.

[4] Most, H., Miller, J. W., Grossman, E. J. *Amer. J. trop. Med.* 1950, 30, 491. Ley, H. L., Sayer, W. J., Hobson, A. C. S., Vanreenen, R. M., Tipton, V. J., Frick, L. P., Ballard, E. L., Traub, R. *Antibiotics Chemotherap.* 1951, 1, 281.

Antibiotic mixtures for amœbiasis have been investigated by Felsenfeld and his co-workers[5] in Chicago, who find that the most effective combination is neomycin and bacitracin; when these were given together for 14 days the subsequent relapse-rate after 3–6 months' observation was only 8·5%. In tests on mice infected with *E. histolytica* neomycin and bacitracin proved only half as active as aureomycin. The most successful remedy for amœbiasis may turn out to be a mixture of antibiotics, or an antibiotic in conjunction with another amœbicide such as chloroquine.

MEDICINE WITHIN THE ATLANTIC COMMUNITY

FROM across the Atlantic comes independent and weighty support for the plea lately put forward in our columns[8] for better cultural contacts within the Atlantic Community. Mr. James B. Conant, president of Harvard University, speaking to the Pilgrims in London on March 19, proposed a "grand academic alliance" among the English-speaking nations. He thought of it as an ellipse, with the capital cities of Great Britain and the United States as its foci, and, ranged round them, the hundred or so university centres of the English-speaking world.

Americans, though they often voice their distrust of kings, princes, autocrats, and potential fathers-of-the-people, are nevertheless more inclined than our committee-loving nation to entrust power to individuals. Thus whenever anyone at Harvard speaks of "the President" everyone knows he means Dr. Conant and not "that man in the White House." And indeed Dr. Conant presides over a vast educational empire, which includes a justly celebrated medical school. A community of understanding among scholars and university administrators, he suggested, would be "one more massive stone in the foundation of good British-American relations," and to achieve this there must be far freer movement of individuals within "the elliptical area" than is possible at present. He recognised the difficulties caused by security regulations, visa restrictions, and money, but he hoped that with time these can be solved. This might be achieved, Mr. D. R. Dudley, director of extramural studies at Birmingham University, has since suggested,[9] by the creation of a new foundation with funds in dollars for the use particularly of senior members of British universities, to be matched perhaps by a sterling fund for the use of American students in Britain.

If such a scheme provided better exchanges between medical teachers within the English-speaking world, it would of course receive the enthusiastic support of British doctors. But Dr. Conant did not mention medicine specifically and he may not have had us in mind. His policy at Harvard has always seemed to favour pure academic scholarship that would otherwise go by default through lack of public support, and in pursuing this essentially laudable policy he is said to have been forced to curtail expenditure on the Harvard Medical School. Obviously, as a contemporary Scots teacher has remarked, "a university must draw the line somewhere between useless knowledge and manual labour." But it is to be hoped that Dr. Conant will agree that medical teaching is more than mere technical and professional training and will be willing to admit some of us to the ranks of the worthy scholars whom his scheme is designed to help.

Dr. Conant made his plea for a better understanding between university administrators with no thought of promoting educational uniformity, still less of imposing American standards on the English-speaking world. As he said "education is not an exportable commodity." He showed a sympathetic understanding of the differing educational needs of Britain and America, and he readily admitted that only 30 or 40 of the 1500 colleges and universities in the United States could be compared to British universities. The United States, as a [illegible] country, he explained, has had to educate many students coming from "homes with a minimum of cultural advantage" without a background of wide reading. A third of the youth of the States are now receiving college or university education, though they are not always engaged in what we would regard as university studies. He thought the universities of the United States needed the counsel and example of the older universities in Great Britain: in return they would like to share their experience with newer universities in Canada, Australia, and New Zealand.

Dr. Conant's sensible proposals are open to one important criticism: they may be too restrictive. Though he denied that a cultural union among English-speaking nations would be a barrier to wider international union, it is difficult to see how "by joint coöperation we should be forwarding international relations among all the nations." Americans find it hard to realise that we have many closer ties with the people of Western Europe than with some who use our language in the heart of the United States. Certainly we in Medicine would not wish to sever our historic contacts with the Continental tradition to which we owe our beginnings. Will not Dr. Conant extend his hand, not only to the British people, but also to our neighbours in Europe who belong to the Atlantic Community?

Prof. EDWIN BRAMWELL, consulting physician to the Edinburgh Royal Infirmary, died on March 21 at the age of 79.

FOUR members of the medical profession are among the 25 newly elected fellows of the Royal Society. They are: Dr. B. KATZ, professor of biophysics, University College, London; Dr. J. S. MITCHELL, professor of radiotherapeutics in the University of Cambridge and director of the radiotherapeutic centre, Addenbrooke's Hospital; Dr. R. R. RACE, serologist, Medical Research Council, Lister Institute; and Dr. MARTHE VOGT, lecturer in pharmacology, University of Edinburgh. The following have also been elected to the fellowship: Mr. N. J. BERRILL, D.SC., Strathcona professor of zoology, McGill University, Montreal; Miss HONOR FELL, D.SC., director of the Strangeways Research Laboratory, Cambridge; Mr. R. LEMBERG, director of the biochemical department, Institute of Medical Research, Royal North Shore Hospital, Sydney; and Mr. D. D. WOODS, lecturer in microbiology, Oxford University.

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5. Felsenfeld, O., Kadison, E. R., Ishihara, S. J. *Amer. J. publ. Hlth*, 1951, 41, 1078.
6. Tobie, J. E., Most, H., Reardon, L. V., Bozicevich, J. *Amer. J. trop. Med.* 1951, 31, 414.
7. Killough, J. H., Magill, G. B. *J. Amer. med. Ass.* 1951, 147, 1737.
8. *Lancet*, Feb. 16, 1952, p. 360.
9. *Times*, March 22, 1952.

Special Articles

THE CONVALESCENT CHILD *

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CONVALESCENCE is difficult to define ; it has no clear boundaries and its content cannot be assessed with precision. Much of our knowledge of it is based on clinical experience and observation, which, though often reliable, is seldom suitable for purposes of comparison. Both in this country and in the United States it is becoming apparent that further investigation and interest are required.

> "There is greater need for a better understanding of both the qualitative and quantitative aspects of such phases of treatment as diet, rest and activity, and far more adequate measures to determine when convalescence is complete" (Nelson 1950).
>
> "Convalescent care in childhood does not yet have the importance attached to it which it deserves" (Craig 1947).
>
> "Convalescent homes as a whole appear to be in much the same state in the U.S.A. as they are in England. There is a committee of the United Hospital Fund for New York which is trying to raise standards by arranging meetings of Matrons and Trustees of convalescent homes" (Simmonds and Peers 1951).

These are examples of the comments being made by experienced pædiatricians and observers.

The Present

Convalescent care for children is accepted to be important after rheumatic fever and many orthopædic conditions ; but many doctors are not alive to the importance of the recovery processes in childhood after every illness. Often the patient is dismissed with too few instructions to the parents, and no arrangements for supervision. Children need convalescence after a short acute illness or acute exacerbation of a chronic illness ; after a long illness ; or after a debilitating illness of medium duration, such as pertussis. A group of children with sociological problems, mental exhaustion or debility states, also require convalescence.

SIX ESSENTIALS

The chief needs of these children are :

Rest.—This is perhaps the outstanding requirement, but it is possible to order too much or too little. Restlessness and unhappiness can be caused by over-restricting children, and we must hold the balance between recovery of tissue by rest and atrophy by disuse.

Increasing, but graded, physical activity.

Diet.—"The dietetic needs of children vary from child to child, and from time to time in any child. An attempt to insist upon a standard pattern, regardless of the dictates of appetite is likely to invite trouble" (Capon 1947). With this wise statement in mind the principles of diet in convalescent care are not difficult to follow. The diet should aim at taking into account the increased need for proteins, vitamins, and minerals. This is especially true for the child who is recovering from a nutritional deficiency or disease.

Formal education.

Play and occupational therapy.

A happy secure environment.—This point is important, as shown by Craig's (1947) observations on the effects of war-time evacuation of children from the great cities. Much physical improvement may accrue, but for full health there must be mental contentment and emotional stability as well.

THE BEST PLACE

Convalescent care may be offered in the child's home, in a foster-home, in a convalescent home, or in hospital—which is rarely satisfactory.

Too often convalescence means moving the child to a convalescent home or keeping him in hospital. But convalescent care does not necessarily imply leaving home ; and ideally convalescence should mean a return to home from the hospital. Usually the child's own home is suitable for short-term convalescence, but long-term convalescence is more difficult. In this country supervised foster-homes for convalescent children have not been developed. This is a pity, for the method has an undoubted place in convalescent care. In France it is being encouraged, and in New York the Speedwell Plan organises foster-homes of this kind.

But properly equipped convalescent homes have proved their worth time and time again. They are at their best in dealing with the long-term convalescent, provided always that the child's psychological needs are kept to the fore. These homes are few, and vary considerably. A recent survey "has laid bare the present nakedness of the land and the strange variety in homes which are functioning at the moment" (King Edward's Hospital Fund 1949).

I have studied in some detail two areas in the British Isles and I concluded that the difficulties encountered are similar in most centres here and indeed in the United States, France, and Switzerland. In these two areas waiting-lists were long—usually a month—and the number of beds fell far short of needs. There were no special arrangements to help parents to provide convalescent care for these children in their own homes. Accommodation for older boys, for infants, and for a baby and mother together was especially lacking.

PSYCHOLOGICAL ASPECT

Treatment must be adjusted to each child—as emphasised by Spence (1947)—and the child's emotional needs must be remembered. Strong evidence has been put forward that separating a child from his mother in early childhood—certainly up to school-age—can cause mental ill health which may last until adult life, or may only appear in adult life or adolescence (Bowlby 1951).

A child convalescing from an illness needs special care for a varying period. With the younger child probably the love and care of his mother is his most important need. The child of under 5 years who cannot convalesce at home should if possible be sent with his mother to a convalescent home. It may be necessary to send the child straight from hospital to a convalescent home without his mother. But many children who have been separated from their mothers while in hospital are sent home for a time, only to be separated once more from their families when there is a vacancy in a convalescent home. Whatever its administrative convenience, this practice is to be utterly condemned.

EDUCATION

The importance of educating the convalescent child, or continuing to educate him, is all too often underestimated. Education is particularly necessary for the long-term convalescent because he will probably have to earn his living by his brains rather than by physical ability. It is comparatively unimportant how much the child learns, provided he is encouraged to create and is prevented from becoming mentally stagnant. Education is also a good form of occupational therapy. Naturally the longer the convalescence the more important education becomes. Around the age of 7 years education is all-important, for at this time the child is about to start schooling in its true sense. A gap here can do untold harm ; for, though he may not be very far behind when he returns to school, he feels he is and easily becomes discouraged.

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* This paper is based on a monograph, to be published by the University Press, University of Liverpool, on research carried out while holding a Cow & Gate research scholarship in the university.

If the convalescent child is kept at home, in all but the shortest periods—say anything over 4 weeks—he should have some lessons. When we are so short of teachers, to suggest that teachers should go round homes where children are convalescing may exasperate those responsible for educating our children, but the recommendation is in fact yet another reason why we need more teachers. A teacher cannot spend long at each child's side, for it is a wasteful method from the point of view of teacher-hours, but visits of encouragement and the setting of tasks are well worth while. Just as much harm can be done, however, by giving the child too much to do; and teachers would do well to consider each child's needs and state of health.

All convalescent homes for children should have a staff of trained teachers. Teaching should be carried out communally and as near as possible in classes. There should be large rooms where beds or mobile couches can be wheeled and the children who are to be kept in bed can be taught in this way. Many teachers questioned during this survey thought the British Broadcasting Corporation schools broadcasts were highly suitable for convalescent children—especially long-term—and were not used nearly enough. Teachers should have some special training for dealing with these children, and should have special hours and holidays to fit their work. At present, I found some teachers in homes are made to take standard holidays all at the same time, thus leaving the children unoccupied for long periods, to the chagrin of the nursing staffs.

CLIMATE

It has become a tradition that a patient recovering from an illness benefits greatly from a period spent at the seaside, or perhaps in the country. This tradition has been applied even more intensely to child patients than adults, but there are few scientific facts to back it, though experience favours certain localities for certain diseases.

At the moment, then, common sense must decide the climate for an ideal convalescence. In other words we can make some negative recommendations and a few general positive ones:

The climate should not have great extremes of temperature.

It should not be unduly damp.

It need not necessarily be in the heart of the country nor by the seaside, but should not be in a smoke-contaminated town area.

It will of course be very pleasant for the children if the home is in the country or by the seaside; but if we are completely open-minded, at the moment that is as far as we can go. On the other hand experienced people who say, for example, "we do find that convalescent pertussis patients on the whole do exceptionally well here," should not be disregarded. More research is needed into the reasons for these opinions.

THE ECONOMIC ASPECT

In these days of shortage of money and nurses planned convalescence can prove a real saving. Bywaters (1950) gives the following startling American figures for rheumatic children.

Relative cost of case:

Home care	30–35 dollars/month
Foster-home care	45–50 dollars/month
Convalescent home	120 dollars/month
Hospital	400 dollars/month

From my survey I estimated that these proportions hold approximately in the British Isles.

	£	s.	d.	
Home care	5	6	8	approximately, per month, per child
Foster-home care	8	0	0	
Convalescent home ..	20	0	0	
Hospital	88	0	0	

At two large British children's hospitals there are 1·1 nurses per bed. The corresponding figure in a well-staffed convalescent home is 0·31 nurse per bed. Thus it costs only a *quarter* as much to keep a child in a convalescent home as in a hospital; and it takes a *third* of the number of nurses to nurse him. The need for skilled nursing is less in the convalescent home and the work can be done by less highly trained people, including voluntary or part-time helpers.

The financial administration of convalescent homes in this country is varied. There are three main types:

1. The convalescent home run entirely by the National Health Service. This is uncommon and is usually, in fact, a hospital providing medical and nursing care for heavy cases.
2. The convalescent home outside the National Health Service but with contractual arrangements with the service. When a child recommended for convalescence is placed in one of these homes, the cost is met by the regional board according to the charge of that particular home.
3. Homes entirely outside the National Health Service who have no contractual arrangements with it. These are either run in whole or part by charitable organisations, or the cost is met by the child's parents or guardians.

By a recent provision under the Education Act convalescence is now free for children of school-age, but only at a home where schooling is provided.

SUMMARY

Any comprehensive health service must include convalescent care. The present haphazard relations between convalescent care and our National Health Service are unsatisfactory.

Too little emphasis is given to convalescent care in teaching medical students, nurses, and ancillary workers. The public should also be taught its value.

Pædiatric centres—e.g., large hospitals or departments of child health—should direct child convalescent care in their areas. Their duties should range from recommendations to general practitioners to the running of convalescent homes of their own.

There is a pressing need for more convalescent homes for children, especially homes which will take the adolescent boy and the infant—and ideally the mother too.

The Future

So much for the care of the convalescent child as I find it today. From my observations here and abroad I would put forward the following suggestions for tomorrow.

Home Visits.—A mobile convalescent care unit, staffed by a medical officer and senior nurse and run from a children's hospital might usefully visit children convalescing in their own homes. The unit would be careful to avoid interfering with the family and home, and undermining parental responsibility, but would offer help and advice in the management and care of the child. It may be objected that the work done by the team should be carried out by the general practitioner. With good housing and ample numbers of general practitioners this could be so. Until these conditions are fulfilled it would be advisable to make a step towards it, at the same time doing everything to encourage the practitioner's interest.

Convalescent Day Schools.—This, as an idea, is an extension of the day schools for invalid children found under the direction of the London County Council and is also modelled on the Condon School in Cincinnati, U.S.A., which is run by that city. Such a school is only practicable in large centres of population.

Besides a teaching staff, a school of this kind would need a daily staff of nurses (or trained child workers), a staffed physiotherapy department, and a consulting-room and small laboratory for the visiting doctor in charge of the school. The building would need lifts to all floors, slopes rather than steps—for wheel-chairs—kitchens and a communal diningo accommodate mobile couches, cots, and wheel- and special lavatory facilities. It must also have e gardens so that lessons could be given in the open n suitable. The children would be fetched from their by special buses.

ped Foster-homes.—The long-term convalescent eeds a special home. The following suggestions forward only as a guide to details which would be worked out in practice.

home would take boys and girls from the age of 3 to lescence. All types of long-term case would be taken tuberculosis cases. The institution would be divided eral houses, each with a family of nine or ten children, a house-mother, and ideally a house-father. The duties ouse-mother and her small staff would include cooking, would not be expected to have any special knowledge ng. Ten of these houses—a hundred children in all— be ringed round a central block of buildings containing s for: medical care, inspection, and follow-up investi- of the children; education; physiotherapy; and care headquarters for general instruction and pro- of visiting nurses to the houses.

idea behind these proposals is to keep the child in with his own home, or at least a good substitute.

ral Convalescent Homes.—These homes would take escent boys and girls from 2 to 15 years. Though should be specialised homes for children with atic disease, orthopædic or neurological conditions, al palsy, and tuberculosis, the general home should pared to take any of these conditions.

ome of this kind should probably have 50–60 beds. n under 2 years should not be admitted unless there are facilities. Boys and girls over 5 are best separated wards and if possible placed in age-groups. Communal and play for both sexes is to be encouraged. A ry of the hospital or doctor's case-notes should be sent he child on admission, and case-notes and follow-up should be kept for each child at the convalescent One of the reasons why research is difficult at present use such notes are hardly ever available. On admission hild should be examined within twenty-four hours by edical officer in charge and immediately before dis- In between, regular rounds should be made by the al officer. It is not necessary for him to be resident must be on call. Consultants should be available. ron or senior sister should be in charge, and five fully d nurses per hundred patients are necessary. At least one d nurse should live in and one should be on duty at all In addition there should be one attendant per ten en. The attendant might be a student nurse, a child- tudent, or a part-time helper with experience.

a home of this kind the pavilion type of ward of twenty nits opening on to a veranda is suitable. These units be repeated a number of times round central services and easy mobility of the patients. Visits by parents should gorously encouraged.

RESEARCH

is doubtful whether any clear scientific indications convalescence exist. "The basic facts of con- cence are not well established. There is a recognised for research on the clinical and biochemical, as well e organisation and social aspects of convalescence" ndards for Convalescent Homes for Children 1948). ould be worth investigating, along clinical and hemical lines, the convalescent period after different ses in a good sample of children. No such work been done. Possible subjects would be: (1) the stigation of physical recovery, giving as instances, ht and stature changes, and biochemical changes in convalescent period; (2) the recurrences of illness ed to the convalescence; and (3) the psychological oach, by means of attempts at assessing intelligence, ral happiness, and well-being in the convalescent od.

wish to thank the medical officers, matrons, sisters, ing staff, and all other staff, of the centres and homes which I visited in Cincinnati, Durham, Liverpool, London, and Zürich. My study was constantly guided, helped, and encouraged by Prof. Norman Capon.

REFERENCES

Bowlby, J. (1951) Maternal Care and Mental Health. Geneva.

Bywaters, E. G. L. (1950) *Proc. R. Soc. Med.* 43, 199.

Capon, N. (1947) Foundations of Health in Childhood. London; p. 50.

Craig, W. S. (1947) *Practitioner*, 159, 95.

King Edward's Hospital Fund (1949) Directory of Convalescent Homes. London.

Nelson, W. E. (1950) Textbook of Pediatrics. Philadelphia; p. 257.

Simmonds, B. S., Peers, R. E. (1951) *Lancet*, i, 844.

Spence, J. C. (1947) *Brit. med. J.* i, 125.

Standards for Convalescent Homes for Children (1948) *J. Pediat.* 33, 251.

EXCITATION AND INHIBITION

ROYAL SOCIETY'S SYMPOSIUM

On Feb. 21 a symposium on Excitation and Inhibition was held by the Royal Society under the chairmanship of Prof. E. D. ADRIAN, O.M., the president. The symposium marked the stay in this country of Prof. J. C. ECCLES, F.R.S. (Canberra), after fourteen years' absence in Australia and New Zealand. His colleagues in Britain could have found no better way of showing their regard for him.

In his introductory remarks Professor ECCLES emphasised that the seven invited speakers would all deal with different aspects of the same problem: the events at a surface membrane of an excitable structure during nervous activity.

ELECTROLYTE CHANGES

Prof. A. L. HODGKIN, F.R.S. (Cambridge), discussed the way in which electrical signals are propagated along the giant nerve-fibres of squids and cuttlefish. These fibres contain a high concentration of potassium ions and a low concentration of chloride and sodium ions—the reverse of the situation in animals' blood. Conduction of impulses is associated with a gain of sodium and a loss of potassium, which have been measured with radioactive tracers. Professor Hodgkin described experiments made in association with A. F. Huxley in order to find out how nerve-fibres use the energy derived from the mixing of sodium and potassium ions to generate and conduct electrical impulses. Their method consisted in measuring the current which flows through the membrane when the voltage across it is suddenly reduced by a known amount. They found that the ionic current through the membrane consisted of a quick phase, which varied with the concentration of sodium ions in the external medium, and a slower component due to outward movement of potassium ions. The changes in the membrane, associated with depolarisation, are a rapid but transient increase in the permeability to sodium ions and a lower but maintained increase in potassium permeability. These rather simple changes are sufficient to account for the action-potential in quantitative terms and to lead to a value for the conduction velocity which is close to that found experimentally.

MOTOR ENDPLATES

Prof. B. KATZ, F.R.S. (London), dealt with the electrical activity of the motor endplate, describing work carried out in collaboration with P. Fatt. Professor Katz pointed out that their experiments with intracellular electrodes had made it possible to measure the quantity of electricity which is transferred across the endplate membrane following the arrival of a motor impulse. Under certain conditions, this quantity exceeds the total ionic charge stored inside the nerve terminals. This rules out all suggestion that ions released, or currents produced, by the nerve-endings may directly provide the observed flux of charge across the motor endplate. The alternative possibility is that acetylcholine reacts with the endplate so as to make it permeable to other ions, and in this way gives rise to a high local current density. Study of the electric responses of the endplate region has provided evidence for this view, and indicates that the primary action of acetylcholine is to "short-circuit" the muscle-fibre at its endplate. The electric response of the endplate differs in at least two important aspects from the response of a nerve or muscle fibre: (*a*) it is induced by acetylcholine and not by an electric current, and (*b*) it involves a membrane short-circuit which leads to simple depolarisation, and not a specific increase of sodium permeability causing a reversed membrane potential.

TRANSMISSION AT THE ELECTRIC PLATES

Closely related to the problem of electrical activity at motor endplates is that of transmission in electric fishes at the electric plates. Prof. A. **Fessard** (Paris) pointed out that it is wrong to assume, as is generally done, that the events at the electric plates mimic those at the neuromuscular junction. There is a fundamental difference. At the neuromuscular junction we observe a composite response; the motor-endplate potential, which *is a simple depolarisation, followed by the* muscle action-potential, which is a reversed membrane potential. The response of the electric plate has not this composite character; it consists of a simple action-potential only.

We can distinguish seven types of electric organs which show striking structural differences. So far the modern electrical techniques have been applied to only two species; these are the electric eel (electrophorus) and the torpedo-fish. Albe, Fessard, and Chargas made the unexpected observation in electrophorus that the plates are excitable to direct electrical stimulation, and that this direct electric response can be dissociated from that of nervous origin. In the torpedo-fish, on the other hand, Fessard was unable to obtain evidence of a true, direct electrical excitability of the plates, even after curare or denervation. This difference makes it clear that the different electric organs do not conform to a single model. In both species the elementary discharge—i.e., the discharge from the single plate—has all the characteristics of a typical action-potential. Despite the extremely favourable conditions for recording, it has not been possible to detect anything resembling the sequence of events at the neuromuscular junction. Only a spike is seen; no intermediate electrical signs of a transmitter action can be detected. Nevertheless, there is the analogy with transmission by acetylcholine. The nerves to the electric plates, like the motor nerves to skeletal muscles, appear to be cholinergic. Experiments carried out before the late war by Feldberg and Fessard provided strong evidence for transmission by acetylcholine. In these experiments it was also shown that acetylcholine arterially injected into the perfused electric organ produced an electrogenic effect. But can we really compare this effect with the discharge; or would this effect be sufficient for the trigger action which, by analogy with the motor-endplate potential, would fire off the action-potential? Professor Fessard suggested that possibly all the oddities of the specific synapses in electric fishes may one day be explained by secondary factors which result from specific chemical, electrical, and structural peculiarities.

EXCITABILITY OF NERVE-FIBRES

Dr. R. **Lorente de Nó** (New York) returned to the question of the nerve-impulse. His view about the rôle of sodium in nerve physiology differed from that expressed by Professor Hodgkin. He agreed that frog nerves kept in a sodium-free medium become inexcitable and recover their ability to conduct impulses after sodium ions are made available to them. Sodium therefore plays an essential part in maintaining their excitability. But he has found that removal of the epineurium greatly sensitises the nerve-fibres to the effect of lack of sodium, and that this change in physiological properties is accompanied by spectacular anatomical changes which are readily demonstrable in histological sections stained with ordinary methods. If such nerves, deprived of epineurium, are placed in a sodium-free medium, all the nerve-fibres become inexcitable within a few minutes (ordinarily 4–6), but when the nerve is removed from the medium the fibres recover their ability to conduct impulses spontaneously. When sodium-free medium is again applied to the nerve, it becomes inexcitable within 1 minute; and when the medium is removed excitability again returns. This phenomenon can be observed with the same nerve five or six times.

The immediate cause of the inexcitability is, according to Dr. Lorente de Nó, not the loss of sodium ions to the sodium-free medium—even though such a loss must take place—but the loss of some substance which is synthesised in the metabolic processes of the nerve-fibres when sodium is available; sodium-deficient nerve is unable to synthesise this substance, or at least to do so at a rate which exceeds that at which it is lost *to the external medium.* The substance in question may be an amine or a quaternary ammonium compound, since both cocaine and certain quaternary ammonium compounds are known to be able to take the place of sodium and restore the excitability of nerve-fibres deprived of sodium.

Years ago a mixture of quaternary ammonium bases extracted from ox brain was shown to restore the excitability of frog nerve-fibres deprived of sodium. Since then extracts have yielded in crystalline form the chlorides of at least three, and probably four, quaternary ammonium bases, one of which is coloured. In alcoholic solution this is pale green in the presence of oxygen, but orange-yellow in its absence. From a solution in propyl alcohol the chloride of this base crystallises in orange-yellow needles.

Dr. Lorente de Nó assumes that these naturally occurring quaternary ammonium bases may be the essential substances for the excitability of the nerve-fibres.

SLOW POTENTIALS IN THE RETINA

Prof. **Ragnar Granit** (Stockholm) presented his results on slow potentials accompanying excitation and inhibition in the retina. Light induces two particularly large changes of potential of opposite character—one, P II, intimately associated with excitation, and the other, P III, intimately associated with inhibition of the discharge in the optic nerve. He paid special attention to the latter, and outlined the discovery of inhibition to light which he and Therman made in 1934. Later work, together with Hartline and Parry, concerning the elucidation of inhibition in the retina was reviewed. Finally, Professor Granit pointed out that the association of opposite potentials in the retina with excitation and inhibition has acquired fresh interest from the work of Professor Eccles, according to which depolarisation and hyperpolarisation of the ventral horn cell is associated with monosynaptic excitation and inhibition respectively. Thus, in the retina as well as in the spinal cord the potential with the inhibitory component appears to be a hyperpolarisation of the membrane.

CHEMICAL TRANSMISSION

Dr. W. S. **Feldberg**, F.R.S. (London), discussed how central excitation and inhibition can be explained by the chemical transmission theory. Can these phenomena be explained, he asked, by one transmitter, acetylcholine, or have we to postulate several transmitters? Theoretically, acetylcholine could induce central inhibition:

1. By over-depolarisation. A condition which certainly occurs under abnormal conditions (for instance, after eserine)

is probably a different phenomenon from inhibition is more justifiably called "block."

By having different actions if released on different s of the cell (for instance, at the soma and at the axon ck). This assumption presupposes a blocking action cetylcholine if released at certain points of the cell.

By having opposite actions at different synapses. It d depolarise one cell and polarise another.

rom the pharmacological point of view, such a ception presents no difficulties. After all, some smooth- cle fibres contract, others relax, to acetylcholine. fact that so far there is no evidence for two kinds erve-cells which act in opposite ways to acetylcholine s not mean that they do not exist. This kind of hanism, however, cannot explain the new findings Professor Eccles that the same nerve-cell responds impulses from different nerve-fibres in opposite s.

onsidering the possibility of different chemical trans- ters, the simplest way would be to assume one trans- ter for excitation and another for inhibition. The blem, however, is more complicated. It is true that tylcholine is not the universal central transmitter; all posterior-root fibres appear to be non-cholinergic, the present evidence of the distribution of cholinergic non-cholinergic fibres does not relate to the problem central excitation and inhibition. Dr. Feldberg not feel justified in discussing the possible rôle of enaline or noradrenaline as central synaptic trans- ters, even though these substances influence central ivity in an opposite way to acetylcholine; for there ot sufficient evidence that they are widely distributed he central nervous sytem.

r. Feldberg then turned to the question whether differ- transmitters may be present in one nerve-fibre, so that en it divides each branch releases a different transmitter. m our knowledge of peripheral cholinergic and adren- ic neurones this appears unlikely, since the property a neurone cannot change in its course. If there are erent central transmitters for excitation and inhibition, y are probably located in different neurones, but the ne nerve-cell can respond to both. If a special central ibiting transmitter exists, its properties of synthesis d destruction probably resemble those of acetyl- line. Synthesising and destroying enzymes would be ated along the whole axon of the neurone. In looking perimentally for such a transmitter, this possibility uld be kept in mind. In fact, one of the main blems of chemical transmission in the central nervous stem is that of transmitter substances other than etylcholine. This problem exists independently of tral excitation and inhibition.

EVIDENCE AGAINST THE ELECTRIC THEORY

The last speaker was Professor ECCLES, who gave account of the fascinating results that he, with Brock and J. S. Coombs, obtained when recording th a micro-electrode from the interior of a motor- rn cell of the cat's spinal cord. These results have him to abandon the electric theory of synaptic ansmission in the central nervous system. Entry the micro-electrode into a motor neurone is signalled immediate negativity of the micro-electrode of about -60 mV; so there is no doubt when the electrode is side the cell. Professor Eccles went on to show, in nvincing records, that monosynaptic excitatory and hibitory volleys in the large group, Ia, afferent fibres oduce opposite effects on the same motor neurone. he excitatory volley causes a prolonged potential ange (the synaptic potential) in the same direction as e spike, and at a critical level this depolarisation nerates a spike which not only abolishes but reverses e resting potential—i.e., the negativity of the intra- llular micro-electrode. The inhibitory volleys in fibres from antagonist muscles, on the other hand, cause hyperpolarisation of the motor neurone. The time-course of this hyperpolarisation, which usually amounts to not more than 2 mV, runs similarly to the excitatory depolarisation. This hyperpolarisation, which directly counteracts the depolarisation produced by the excitatory synaptic action and which is the cause of the inhibitory effect, cannot be explained by any known response of the nerve membrane to applied electric current. Professor Eccles therefore no longer agrees with the electricæ theory. Inhibition is presumably caused by a specific chemical mediator which acts by greatly increasing the net outward flux of cations; and then excitation will also be attributable to a chemical transmitter which causes a net inward flux of cations.

EARLY WORK BY GASKELL

Sir HENRY DALE, O.M., F.R.S., who opened the general discussion, remarked that in 1886 Gaskell showed that the inhibitory effect of vagus stimulation on the isolated non-beating auricle of the tortoise was associated with an increase in the demarcation current—an increase in positivity or, as we would now call it, hyperpolarisation.

HEALTH SERVICE ESTIMATES

THE National Health Service estimates for 1952–53,[1] issued last week, set gross expenditure on the service for the whole of Britain at £475,814,500 in the coming financial year, compared with £470,551,200 in the present year. After deduction of appropriations-in-aid (e.g., from National Insurance contributions) the net cost to the tax-payer is expected to be £402,286,500, compared with £399,506,500 in the present year.

At first sight it seems that the service is exceeding the £400 million limit to which the Chancellor, like his predecessors, is pledged. In fact, however, expenditure on the Civil Defence services (which is included in the N.H.S. estimates) is to increase steeply from £1,188,000 this year to £10,047,200 next year; and thus expenditure on the health service proper is well within the £400 million limit.

Though the aggregate expenditure remains much the same, substantial changes are evident in the allocations under the various heads. Thus the allocation to the hospital, specialist, and ancillary services is to be increased from £284,738,400 to £304,415,300 (with a decrease in the amount allotted to capital expenditure), and grants to local health authorities from £18,509,500 to £21,223,000; while expenditure on the general medical and dental services, pharmaceutical services, and supplementary ophthalmic services is to be reduced by £28,058,800 to £118,669,700. Under this head the figures for the coming year and the present are as follows:

	1952–53 (£)	*1951–52* (£)
Administration	2,736,000	2,961,000
General medical services	48,500,000	48,400,000
Pharmaceutical services	39,950,000	43,610,000
General dental services	20,150,000	36,200,000
Supplementary ophthalmic services	6,300,000	14,650,000
Other expenses	1,033,700	907,500

The actual cost of the pharmaceutical services is expected to increase in 1952–53 to £47,540,000; but this is offset by the receipt of £7,590,000 from the proposed prescription charges to patients. In the dental services charges to patients, expected to total £10,930,000 (compared with £4,750,000 this year), account for some of the decrease; but under this heading gross payments to dentists are also expected to fall from £40,950,000 to £31,080,000.

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[1] Civil Estimates for the Year Ending 31st March, 1953. Class v: Housing, Local Government, Health, Labour, and National Insurance. H.M. Stationery Office. Pp. 172. 5s.

REMUNERATION OF GENERAL PRACTITIONERS

RESULT OF ADJUDICATION

GENERAL practitioners in the National Health Service draw nearly all their remuneration from the Central Practitioners' Pool. The terms on which this pool is calculated have never been agreed between the Government and the profession. From the start of the National Health Service in July, 1948, the Government have paid into the pool each year a sum arrived at by allowing 18*s.* for 95% of the population; but the profession, especially through the General Medical Services Committee of the British Medical Association, has repeatedly declared that this sum is inadequate, especially as it now has to be divided among some 20,000 practitioners in the N.H.S. instead of the 17,900 assumed in 1948. The criterion which both sides accept is the report of the Spens Committee on the Remuneration of General Practitioners; but this committee, in making a clear statement about the range of incomes appropriate for practitioners at 1939 money values, added:

> "We leave to others the problem of the necessary adjustment to present conditions, but we would observe . . . that such adjustment should have direct regard not only to estimates of the change in the value of money but to the increases which have in fact taken place since 1939 in incomes in other professions."

The "betterment factors" added by the late Government in making this adjustment were 20% for net income and 55% for expenses; but these percentages have never been regarded by doctors as reasonable.

Last summer the Government offered to add £2 million to the Central Practitioners' Pool; and the Conference of Local Medical Committees, in rejecting this offer, demanded arbitration. In August the Minister of Health and the Secretary of State for Scotland agreed to arbitration on condition that a working party was set up to devise a new plan for the distribution of the Central Pool so as to discourage practitioners from having unduly large lists and at the same time "to bring about a relative improvement in the position of those practitioners least favourably placed under the present plan of distribution, to make it easier for new doctors to enter general practice, and to stimulate group practice."

The task of adjudication between the Health Ministers, on the one hand, and the General Medical Services Committee, on the other, was entrusted to Mr. Justice Danckwerts, and his inquiry was held in London between March 15 and 21, evidence being presented by counsel for the committee and by the Attorney-General and others for the departments. On behalf of the committee it was submitted that to give effect to the Spens Committee's recommendations the betterment figure in 1950–51 should have been 120%, and that the Central Pool for the year ended March 31, 1951, instead of the actual figure of £41,533,000, should have been £57,378,000.

REPORT OF ADJUDICATOR

On March 24 Mr. Justice Danckwerts delivered his findings:

"My Terms of Reference are as follows:—

To determine the size of the Central Pool, after taking account of remuneration from all other sources received by general practitioners, in order to give effect to the recommendations of the Spens Committee, having regard to the change in the value of money since 1939, to the increases which have taken place in incomes in other professions and to all other relevant factors.

"My determination is that the size of the Central Pool for the year ending on the 31st March, 1951, should be £51·252 millions. As was agreed at the hearing, an adjustment to this figure will have to be made in respect of Exchequer superannuation contribution. In order that this determination may be applied to other years, I add the following explanations:

(1) I have applied a betterment factor of 100% to the figure of £19·80 millions for 1939. In my view, the corresponding factor in 1948 would be 85%.

(2) The figure which I have reached has been adjusted by reference to the number of doctors in the National Health Service and not the population. There was no evidence before me that an unnecessarily large number of doctors is likely to enter the Service within the next few years, but if the number of doctors in the Service became unreasonably large this point would require reconsideration.

(3) I have excluded interest on compensation moneys from consideration.

(4) I have excluded from the credits which had to be deducted in determining the size of the Central Pool the amount of the inducement fund in respect of unattractive areas.

(5) I have taken a percentage of 38·7% for expenses. But I have not accepted entirely the figures to which this percentage should be applied.

HAROLD DANCKWERTS."

Parliament

QUESTION TIME

A Pædiatric Practice

Mr. S. S. AWBERY asked the Minister of Health if his attention had been drawn to the experiment of doctors for children only which had been going on for the past few years in Bristol; and if he would inquire into the benefits of this system of medical treatment for children with a view to encouraging it.—Miss PATRICIA HORNSBY-SMITH replied: The Minister is aware of this experiment.[1] It depends for its success on the special interest of a particular doctor, and the Minister doubts whether it is suitable for general application except possibly as a development of group practice.

Food Hygiene

Replying to a question by Dr. A. D. D. BROUGHTON, Major G. LLOYD GEORGE said he regretted that owing to the pressure of Parliamentary business it was not likely to be possible to introduce further legislation establishing a standard of hygiene in catering establishments. He recognised the importance of the matter and was anxious that legislation should be brought forward as soon as possible. In answer to a further question he added that the general policy followed by his predecessor in regard to the clean handling of food was being continued and developed by the present Government.

Dangerous Drug Offences

Replying to a question Sir DAVID MAXWELL FYFE, the Home Secretary, said the number of convictions under the Dangerous Drug Acts for the years 1949 and 1950 were 15 and 147 respectively. The provisional figure for 1951 was 234. He was satisfied that everything was being done to deal with this matter. He believed that some of the increase in convictions was due to increased vigilance on the part of the Police, Customs, and Dangerous Drugs Inspectorate. There was still no sign of regular, organised, widespread illicit traffic.

Experiments on Living Animals

In answer to a question Sir DAVID MAXWELL FYFE said that the present establishment of inspectors under the Cruelty to Animals Act, 1876, was in his view adequate for the proper supervision of experiments to which the Act applied.

Mr. ERIC JOHNSON: Does the Minister really suggest that visits to 1232 out of 1,779,215 experiments carried out on living animals provided an adequate safeguard. Would the inspection not be better done by veterinary surgeons rather than doctors? —Sir DAVID MAXWELL FYFE: The most important thing is that the inspector can visit a laboratory at any time without warning and demand to inspect the animals and see notes of the experiments.

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[1] See *Lancet*, Feb. 23, 1952, p. 412.

Reconstruction

THE RIGHT PATIENT IN THE RIGHT BED

FROM A CORRESPONDENT

Now that the cost of maintaining a patient in an acute hospital is so high, people are beginning to wonder, and not for the first time, whether we should not economise by providing other accommodation for some patients. Should not postoperative or convalescent cases, for example, and the borderline chronic, be passed on to less expensive accommodation so that the beds they occupy can be set free for others?

There is, of course, much to be said for the doctrine of "the right patient in the right bed" if it is applied with intelligence. The need to secure better classification of patients, so that only those who really require the exceptional facilities of expensive diagnostic or therapeutic units are drafted into them is widely recognised, and this approach underlies much of the reorganisation now being carried through by the hospital management committees with their different categories of bed, and by the regional hospital boards as they work towards the organisation of specialist centres. More can certainly be done in this direction, notably by the provision of homes for the aged sick and for other patients for whom hospital treatment is not strictly necessary at all. Obviously it is highly uneconomic to allow such patients to occupy beds which are needed for hospital purposes.

But how far can the principle be taken? It is easy to carry the argument so far as to make nonsense of it. Whenever the search for economies is being pressed specially hard, as it is today, there are to be found advocates of a more extensive provision of the cheaper categories of recovery or convalescent beds. They rely on variants of an argument which runs like this: "In the large general hospital the bed costs £20 per week; now we espy there patients—postoperative or convalescent, let us say—who could be adequately accommodated for £5 a week in a separate home or hostel. Ergo, let us provide such hostels and thereby save some £15 per week." Thus, to quote a classical instance, Lord Cave's committee in 1921 suggested "the cost of new accommodation might be substantially reduced if the main buildings could be restricted to the accommodation of cases requiring constant medical or surgical supervision, and the less serious cases were removed to an auxiliary hospital on the outskirts of the city," which would be "less expensive to build and maintain," while recuperation would be "pleasanter and more rapid."

AN ECONOMIC FALLACY

This argument, in one form or another, is continually cropping up, but it is largely fallacious. For consider. In the large multi-purpose general hospital patients cost varying amounts—in some departments more, in others less—and the so-called cost per patient per week is an abstract calculation, a mere average figure. It is quite unscientific to pick out particular groups of patients, or patients at particular periods of their stay, and assume that after making other provision for them and replacing them with other patients the average cost for the whole hospital would remain unaltered. The cost of £20 is only what it is by reason of the presence of these £5-a-week patients. True there may be some overheads which would not increase; but to bring this factor into the picture is to plunge into complicated calculations, and the end-result could only be determined by a costing system as elaborate as that which guides Lord Nuffield in distributing work among his factories.

The supposed saving will in fact be achieved only if a number of somewhat unlikely conditions are fulfilled. If, for example, the expensive diagnostic and therapeutic services are working below capacity, because the number of beds allocated to these departments is inadequate, it may be possible to increase their load without proportionate additional cost. But this amounts to a fresh proposition, involving the replanning of the whole service and a fresh calculation of costs. There will be no saving unless there are corresponding reductions in expensive facilities elsewhere. The point was put in a King's Fund report of 1928 in a discussion on recovery homes:

> "The addition of a recovery branch concentrates in the parent hospital a larger number of patients who need expensive methods of diagnosis, operations, and other early stages of treatment, and thus enables fuller use to be made of the highly specialised staff and apparatus, thereby reducing cost and increasing efficiency of service. But this result is only produced if the staff and apparatus are not already fully employed, and in that case would be produced by the addition of beds on the hospital site."

On the whole it was felt that the advantage of the system, apart from any effect on cost of site or building, lay not in any reduction of maintenance costs, but in the benefit to the patients of being in the country.

SOME PRACTICAL DISADVANTAGES

To reserve all the beds for acute cases would also have serious disadvantages for the nursing staff. The work of a ward would become so heavy that more nurses would have to be provided and costs would increase. To follow a case through is an important part of nurses' training, and even if the student nurses were seconded to the recovery home they would *not* see the same patients all through their illness. If it should not be possible to second the student nurses to the recovery home there is the added disadvantage that they will have no experience of the convalescent patient. On the other hand, it is more difficult to get good trained staff for a recovery home, because the work is less interesting from a nursing point of view. At the same time the trained staff at the main hospital are probably finding the work too heavy and breaking down under the strain.

If the recovery home is any distance from the main hospital it will be difficult to get the medical staff to pay regular visits. It will also be difficult to attract junior resident staff because of the less interesting work. Most patients are probably quite happy once they are settled in the recovery home, but there is no doubt that they hate the idea of the move.

The subject clearly needs more thought than it has hitherto received. The hospital, it must be recognised, is built up of departments whose cost varies considerably, and in fitting the departments together many complicated considerations come into play. Proper costing certainly does not rule out as uneconomic the inclusion of departments providing simple and relatively inexpensive treatments in buildings which can, and do, also provide the more expensive. What is needed is a departmental analysis of expenditure. When once we have it, and have accustomed ourselves to thinking in terms of departmental costs rather than in those of the obsolete average cost per bed, many of the absurdities for which misuse of the latter is responsible will dissolve.

As opinion stands today it would seem astonishing to many if it turned out to be *more* economic to nurse the chronic sick in units deliberately provided for them within the walls of the large general or teaching hospitals than in the simplest hostel that had to meet all its own overheads. Impossible? A little thought will soon convince the sceptical that they have been making all sorts of assumptions for which there is no basis. The "average cost per bed" is a plausible basis for notions about keeping expensive hospitals for expensive patients. But it is a highly unreliable one.

Medical Conferences

PROJECTS FOR RESEARCH ON MENTAL HEALTH

CONFERENCE OF THE MENTAL HEALTH RESEARCH FUND

AN inaugural conference of the Mental Health Research Fund, held at Magdalen College, Oxford, on March 19–22, with Sir GEOFFREY VICKERS in the chair, set out to answer the questions:

> "What are the ignorances which today principally hamper our understanding of the nature, prevention, and cure of mental illness? *What advances in research are most likely to remove* these, and so help to reduce the population of mental hospitals and institutions for delinquents?"

Our ignorances are so numerous and massive in every branch of this subject that no speaker found himself gravelled for lack of matter, and the following account attempts only to give points from the discussion rather than to review all that was said.

Prof. D. R. MACCALMAN, in the opening address, remarked that his hearers were dealing with emotionally charged, culturally loaded attitudes, feelings, and, thoughts, and with the complicated interplay of events in the life-span of men; and reminded them that they too were human, and liable to be moved. At this conference, he hinted, the good clinician and the good scientist might well compose their differences and learn from one another. Whether as a result of his encouragement or through the beneficent influences of Magdalen in spring, just such a desired harmony prevailed; and (no lambs being present) lions from every department of the study of mind lay down with lions.

NEURO-ANATOMY AND PHYSIOLOGY

Prof. W. E. LE GROS CLARK, F.R.S., reoriented the subject of neuro-anatomy for many of his hearers by directing their attention from the cerebral cortex to the older parts of the brain. Many of these have long been classed together under the conception of the "rhinencephalon," including not only the olfactory bulb and tract and its termination, but such diverse structures as the hippocampus, cingulate gyrus, retrosplenial cortex, hypothalamus, parts of the thalamus, the habenular nucleus (related to the pineal body), the faciculus retroplexus, amygdaloid nuclei, medial forebrain, and others. The study of these structures has been shelved for some time as not worthy of attention from *microsmatic* man. There has also been a tendency to correlate cognitive thinking with the cortex, and affective processes with the autonomic system; but we have come to realise that intellectual and emotional experiences are intimately and inseparably locked, and that if the cerebral cortex is thrown out of gear with those more primitive parts of the brain which provide the neural basis for emotional reaction, its function may become grossly deranged. Mental illness, indeed, is generally recognised to be primarily the result of deficits in the affective rather than the purely cognitive mechanism. Much of the so-called rhinencephalon has proved to be a complex mechanism concerned with emotional processes, and may therefore have an extremely important bearing on mental illness. Experiment has already shown that localised lesions in the hypothalamus (through which, it seems, the amygdala and hippocampus influence emotional behaviour) lead to profound changes in the normal electrical activity of the cerebral cortex; and its intimate nervous and vascular connections with the pituitary gland indicate its relation to the coördinating activities of the endocrine system. New work on the hippocampus suggests that it links the hypothalamus with the cerebral cortex by way of the fornix and the mammillary body; and this circuit—which not only transmits the resultants of cortical activity to the hippocampus but also carries back to the cortex the resultants of hippocampal activity—is only found in mammals, and may be a means of maintaining, or prolonging, the activity of the brain as a whole at the functional level of the cortex. Moreover, the dense matrix of small cells in which the fibre laminæ of the brain are embedded no longer appear as the packing material we were taught to think them, but form a reticular system throughout the brain-stem which seems to exert a controlling influence on the rhythmic electrical activity of the whole cortex. Stimulation of the thalamic reticular system in animals may produce attacks closely resembling petit mal in man. The wakeful state, and indeed the very phenomenon of conscious awareness, may not be mediated by the cortex after all, but by this exceedingly primitive reticula system. The cortex thus appears as a sort of scannin mechanism which the primitive system employs fo its own ends—a calculating machine operated by much more fundamental organisation in the thalam and brain-stem. He also hinted at possibilities of "neuro secretion" in the hypothalamus, akin to the secretion o colloid material in the hypothalamus of lower vertebrate The pineal body, too, has exploded its reputation as vestigial third eye, and appears frankly as a mystery The older parts of the brain are thus presenting oppo tunities for research likely to occupy several generations and they enrich the prospect by being not only comple but exceedingly awkward to get at.

Dr. JOHN BATES, who has been studying the operati treatment of epilepsy, especially when it is associate with the condition known as infantile hemipleg discussed the function of myelinisation of the centr nervous system. It seems, from recent research, tha a myelin sheath enables more impulses to be conducte for a given energy expenditure, and for conduction to b faster; but we know little about conditions among th small myelinated and unmyelinated fibres in the centr nervous system—to what extent, for instance, they a influenced by electrical spread, or how to account f rhythmical behaviour in a system of neurones. Recover of function in the central nervous system also need further study: do undamaged areas "take over, or is the initial loss of function due to wide effects outsid the area destroyed which presently subside leaving onl a residual loss of function from the cells actuall ablated? He mentioned the use of stereotactic instr ments designed to enable the neurosurgeon to plac blind, a recording, stimulating, or cauterising electro in the thalamus and subthalamus. Systematic investig tion of the molecular structure of drugs having ant convulsant properties might be rewarding. He w cautious about the functions of the reticular syste recalling 5 cases seen in the 1920s, where seve lesions (such as pinealomas) had completely destroy the reticular substance in their neighbourhood. T patients had shown such things as ocular palsies, b no mental symptoms whatever.

In the discussion which followed it was felt that the was a danger in drawing an inference from evide of this kind, for in the '20s information collect about the state of consciousness of patients was not detailed as it would be today. Some doubt arose ab the proper training of the men who are to use the n tools needed to extend our range of information: sho they be thoroughly grounded in electrical techniq or could they get on without detailed knowledg And should they be left to pursue their own intere or should they be invited to solve the problems of other Dr. W. MAYER-GROSS suggested that as there are w fields of ignorance, a few complicated techniques, a a very few people still interested in clinical proble clinician should be allowed to put his problems the neurophysiologist. Dr. T. McLardy thought at a man doing electronic work could manage very ll if he had a competent technician at hand to spot lacies; and another speaker remarked that people th scarcely a smattering of physics could be very rned about their gramophones. There is, he suggested, great future for dilettanti in neurophysiology, if can encourage specialists to be dilettanti.

SOCIAL PSYCHOLOGY AND GENETICS

Discussing social research and psychiatry, Prof. BREY LEWIS drew attention to the information ined from large-scale surveys. We need to know e status and cultural context of patients admitted to ental hospitals, and to assess whether treatment is ught primarily because the patient's deviation is rious as an illness or because it produces conspicuous cial behaviour. We must also know more about e attitude of ordinary people to various sorts of mental ness, and to mental hospitals and those who work them; for though these are subjects on which we have pinions, we lack exact information about them. In any instances statistics which have not been worked pon could be used. For other surveys we need the rmission and confidence of those to be investigated. e do not know what happens to patients with various ental disorders after they have left the doctor's care, d whether their recovery was due to therapy, to cial or cultural factors, or to their inherent capacity. difficulty is that patients vary in their willingness o coöperate, and any advantages offered them must enerally be remote, contingent, or altruistic. He did ot advocate that treatment should be offered as a bait: fact he thought "No social research without therapy" thoroughly bad catchword. But he thought that as oon as a procedure had been shown to be not harmful, nd designed to answer a specific question properly, should be supported by the appropriate Government epartment.

Dr. A. T. M. Wilson, having forsaken the respectbility of a laboratory to work with patients, was in avour of a research policy geared to practical needs. ince we cannot back every horse we must be content o put our money on a few, and recognise frankly that out of 10 will be losers. The social sciences are four r five hundred years behind the natural sciences, but hey are at least obliged to contemplate the relation of he researcher to his field from the beginning.

Dr. Eliot Slater believed that research should be applied in fields, not where ignorance is blackest, but where the methods available are most reliable. Genetics is an example of a reliable method capable of contributing exact data to ætiology. It has shown, for example, that Huntingdon's chorea depends on the presence of a dominant gene, and nothing is going to change that small hard fact. Moreover, it has established almost decisively that schizophrenia is not on a par, genetically, with the affective psychoses, and that there is not, as is often supposed, a graded continuous transition between these two types of psychosis. This finding, however, has not been received sympathetically, he thinks, by clinical psychiatrists. Genetics suggests that other qualitatively different conditions can be picked out. For instance, evidence is accumulating that the involutional melancholias are a heterogeneous group; some, especially those with paranoid symptoms, are probably schizophrenic. Genetical studies can be combined with any kind of work on mental health whatever, whether clinical, neurophysiological, or biochemical.

Dr. John Bowlby noted that the connection between the psychopathic personality and separation from the mother in the early months of life is now established. The organisation of perceptual and behaviour patterns seems to pass through critical phases, during which these patterns are highly plastic, and after which they become comparatively rigid. He compared the process with the growth of cells in the embryo, where it is known that their differentiation is influenced by the particular environment in which they find themselves at a particular stage of development. Observation of birds and fishes suggests that complex social behaviour is built on a limited number of ready-made responses; and in the same way the archaic responses of the child probably form the foundation on which adult behaviour is built. Mental illness may depend on flaws in the structure as the building is done.

Prof. T. S. Simey remarked that we have lately discovered the family as a factor in social development, but that we are apt to oversimplify its structure. In Liverpool a study of 48 families elicited that 23 consisted of parents and children; 19 included, in addition, some of the mother's relations; 2 included some of the father's relations; and 4 were miscellaneous. Much work lies ahead in the study of the family and the cultural background.

Prof. J. Elkes pointed out that psycho-analysis began its task by looking, as it were, through the wrong end of the telescope—looking back at the child through the experiences of the adult. Now we are studying the child and seeking clues to his development through the behaviour and maturation processes of animals. We must learn, he said, to tolerate uncertainty. Certainty is a yoke left on our shoulders by the nineteenth century; but it is better to be uncertain and wonder than to be certain and explain.

Dr. J. M. Tanner emphasised our need for studies of normal behaviour and development. We need, he said, an Institute of Human Behaviour to study, especially, families. General practitioners should also be invited to join in research on the family, for they have access to material out of reach of everyone else.

ANIMAL STUDIES

Prof. Roger Russell has been studying experimental neuroses in animals. These are produced when animals trained in one pattern of behaviour (such as the need to seek food in a certain bin) are subjected to a punishment—a blast of cold air, or an electric shock—which alarms them just as they are about to achieve their goal. The "neurotic" behaviour may include useless forms of trial-and-error, reversion to previously discarded patterns, tics, aggression, timorousness, disturbances of respiration and pulse, or other signs. The precipitating factor is conflict, but another essential factor, present in all the successful experimental techniques, is restraint of voluntary movements, either by a harness, or by the subject's own learned patterns of movement. In the absence of such restraint the animals develop no disorder. There may be a spread so that stimuli other than those originally producing the conflict produce the abnormal responses. But not all the animals tested develop behaviour disorders under conflict. Some are resistant to stress, and it has been possible to breed two strains of rats, one very resistant and one very susceptible to breakdown.

A speaker asked at what stage the susceptible rats were removed from their neurotic mothers; and on learning that this was done at weaning feared they might have acquired their susceptible behaviour as a cultural pattern. Dr. Bowlby, however, said that litters of dogs, bred on comparable lines, have been exchanged at birth; and the genetic differences have been found to stand up to the change of social environment.

BIOCHEMISTRY, ENDOCRINOLOGY, AND PHARMACOLOGY

Dr. Derek Richter spoke of the effect—evanescent but striking—of 'Sodium amytal' in recalling to a normal state a semistuporous patient with schizophrenia. Other drugs have similar effects, indicating that metabolic factors are at work in mental illness. The brain is made up of many chemical substances—proteins, enzymes, nucleic acid, phospholipins, and others. By new methods with radioactive tracer elements we can hope to see where an element—such as phosphorus—goes in the brain, and how it combines with phospholipins. Experiments have already shown that, if an animal is given such a tracer and then excited, the pathway taken by the phosphorus molecule is different. It is possible in this way to study changes in brain metabolism in anæsthesia, and convulsive states (for instance after electroconvulsive therapy). A biochemist joining a research unit doing such work may not be interested in the brain at the outset, but the technical problems catch his imagination, and he is soon making his contribution. The biochemical approach is close to treatment, and in 10–20 years may have something to say about it.

Dr. MAX REISS had compared the thyroid indices of patients in the Bristol mental hospitals with those of normal controls, and found the spread much wider in the former group. In fact about 20% of the mental-hospital cases had recognisable thyroid dysfunction—whether hyperfunction or hypofunction. In more than 200 patients showing dysfunction the thyroid index was measured after different treatments and after remission; and it was found that in a statistically significant proportion improvement in the mental state was associated with improvement in the thyroid state. Moreover some encouraging results followed therapy on the basis of thyroid treatment only. The adrenal cortex function of mental patients is now being studied by modern methods.

Professor ELKES discussed the effects of some of the "fantastica"—cannabis, amphetamine, mescaline, and lysergic acid—which produce intoxications in some way resembling psychoses. These offer one line of study. Another is through cell metabolism in the nervous system, and an understanding of the enzyme constitution of neurones and the mode of action of drugs on them. A start has been made, in the identification of neurohumoral substances in the central nervous system, with acetylcholine, but other substances may be equally important. Micro-electrode techniques, recording from single neurones, or small numbers of neurones can be used alongside electro-encephalographic methods. Stereotactically placed subcortical electrodes can be used, and drugs applied by inhalation (so that the conscious unrestrained animal is unaware of them) or by injection.

Prof. F. C. HAPPOLD had made a study of the acetoin level in the plasma in mentally ill patients, and had found it significantly raised in manic-depressives during the depressive phase, while the 2–3 butylene glycol remained at the normal level, so that the two levels, charted on a graph, were roughly parallel. In the manic phase, however, the acetoin level fell significantly lower than normal, while the 2–3 butylene glycol level was significantly raised, and the two lines on the graph crossed over and changed places.

A SUMMING-UP

Prof. ALEXANDER KENNEDY, suggesting lines which research on this luxuriant subject might follow, urged first the claims of the central nervous system to be thoroughly charted, anatomically, physiologically, and chemically. In the clinical field the largest gap is in the study of states of consciousness. More genetical studies are needed, more social research, more studies of experimental neurosis, and the organic side of delinquency. We need, too, some common record system, and a centre where workers in the universities can exchange material. He was supported by Dr. R. STRÖM OLSEN, who favoured the establishment of a genetic bureau, and of research units in mental hospitals. Professor MACCALMAN, who had had the first word, also had the last. The disciplines, he said, are looking for newer and more accurate instruments; but we must look to the men behind the instruments. And all this talk of brain must remind us that the person-to-person instrument used by the clinician is more delicate and accurate than it has sometimes been thought to be.

The proceedings of the conference are to be published by Blackwell Scientific Publications.

Public Health

Will Diphtheria Vanish?

IN England and Wales last year, diphtheria deaths numbered only 32 and notifications 699. Dr. W. P. D. Logan, chief medical statistician of the General Register Office, has, however, given a warning against allowing the immunisation campaign to slacken.

"The situation," he declared, "is now being reached—a situation scarcely dreamed of in 1940 when the immunisation campaign started—where the eradication of diphtheria as an indigenous disease in this country can be foreseen as a very real possibility within the next few years, providing there is no slackening in the immunisation efforts that have been so dramatically successful in the past ten years . . . a vigorously continued immunisation programme, combined with existing methods of epidemic control, may free us entirely from the disease except for the occasional imported case."

Dr. Logan estimated that if a non-immunised child catches diphtheria his chances of dying from the disease are seven times greater than those of an immunised child.

Influenza in Glasgow

Whereas England and Wales have this winter experienced no outbreaks of influenza, Glasgow has had a definite outbreak which began in the first week of February and is now almost over. Serologically the causative organism has been proved to be virus B.

The prevalence is reflected in the weekly totals of first certificates of sickness rendered to the Ministry of National Insurance. These rose from 2991 in the week ended Jan. 1 to a maximum of 9772 in the week ended March 4 (they now number only about 3000 per week). During this period there is normally a seasonal rise of 4000 per week; and more than half of the excess is judged to be due to influenza. Notifications of primary pneumonia rose from 99 in the first week of January to 300 in the week ended March 8. Notified cases of influenzal pneumonia, (which was almost absent in January) numbered 36 in the third week of February.

The spread of the disease across the city was remarkably slow. On the south side the peak number of absentees from school was reached three weeks before the peak on the north side. Some schools had a maximum absenteeism of 25%; and 15–20% was common. The number of people that have been affected is set at 70,000–100,000 (10% of the population).

All age-groups have been involved, but notably children over 5 years of age and adults. The temperature at the onset has been 100–103°F. The illness has lasted three to four days, and has been characterised by running nose and eyes, feverishness, headache, sore throat, laryngitis, pains in the limbs, and sometimes epistaxis. In some cases relapse has followed after seven to ten days, with cough and occasionally gastric disturbance. Deaths have been few.

Variola Minor in Lancashire

During the week ended March 22, 16 cases of variola minor were notified in Lancashire. All are associated with the focus in Rochdale, and arose either in Rochdale itself (10) or in its neighbourhood (Whitworth [4], Heywood [1], and Milnrow [1]). The 4 cases in Whitworth—the first in that district—are believed to have been infected by a missed case in Rochdale that was originally diagnosed as "food rash." Littleborough, where 1 case was notified in the week ended March 8, is now thought to be free from infection. There have been no deaths.

In England Now

A Running Commentary by Peripatetic Correspondents

My tropical hospital must be unique in many ways. Most of our patients come from the Nile swamps and the little patches of dry land found among them. From the cattle-camps they have to travel 200 miles, and sometimes more, to hospital and they bring their relations as well. The province covers about 90,000 square miles, and in the dry season they invade the hospital in hundreds. They speak five or six languages, but fortunately translators are not essential, for their diseases are advanced and the diagnoses obvious. They wear no clothes, if any, and immediately they arrive they scramble round the doctor, proudly exhibiting their large hydroceles, venereal lesions, and so forth, making no attempt to hide conditions that most of us would regard as discreditable.

At the height of the dry season we had over 600 of them in the 250-bed hospital. Feeding them was difficult, but somehow we found 1000 pints of milk a day, with meat, grain, and vegetables, cooked it all, and managed to distribute some to everybody. There had to be daily checks to make sure that they were all there and that no extra ones had come in the hope of free food. With their wives and families, the patients just squatted wherever we could find room for them. The fortunate ones who had been operated on were moved out of the wards as quickly as possible, and the rest queued to take their places. They would follow us round the hospital, asking when their operation was to be done, or when they could have their next injection. The keenest even came to my house. The wives carried reed baskets on their heads filled with sustenance for the journey to hospital—gourds, firewood, tobacco, pipes, beer—and the baby as well. The baskets had to be filled again for the return journey, but by us this time.

In the evenings the hospital compound presented a lively and happy scene. Tribal and family units squatted round their little fires, eating their hospital food, which they all kept for the evening meal, smoking, and keeping up a continual hum of conversation and laughter. There were, of course, occasional emergencies, as when an old man had both his cataracts operated on and then got acute retention, so that he had his prostate out as well. Another fell down the excavations for the foundations of a new building and broke his leg. But somehow or other we got through, and eventually they departed—by steamer, by lorry, or walking—on the long journeys to their cattle-camps and little family villages.

Now that the rains have come and the tumult and the shouting have died, I cannot help comparing our busy season with what I read in the medical journals from home. Here is medicine in the raw, really doing something for the really ill. One is far more of a general doctor than any at home, though our standards may be lower. The laboratory stuff is limited in scope, the X-ray films have to be taken and developed by the doctor himself, and I act as both consulting physician and consulting surgeon for the other three doctors; yet some useful work gets done. Much more ought and could be done, no doubt, but is not that also true at home today and ever since medicine started? Our equipment would not satisfy the young doctor fresh from some great teaching hospital, and our patients would defeat him before he made his diagnoses. But there are chances in tropical countries to practise medicine without these modern aids; to do some real good to suffering humanity; and—for the right kind of man—to enjoy life.

* * *

My colleague of March 1 has not kept up with the advances of science as applied to the de-icing of pipes in the roof. His trouble came from too little lagging; ours from too much. The exhortations of the scientists, together with the financial savings promised by the makers of insulation materials, induced us to wrap up all the hot pipes in our roof space. We used stuff that looked and behaved exactly like plaster-of-paris with hairs in it. Pathology not giving one much practice in making plaster cases, our pipes now resemble a severe example of varicose legs done up in Unna's paste. But they keep all the heat in, and after the one bad frost we have had this winter a length of the unwrapped cold pipe was frozen solid.

Blow-pipes are dangerous in the roof (anyway, someone has stolen ours), and the idea of wringing out hot fomentations a few inches above a plaster ceiling is no more attractive. But prolonged research revealed both a method and a sign of success. The method is to wrap the offending organ with a damp cloth and then massage it with an electric flat-iron. In this way you get exercise which keeps you warm, and the pipe gets its fomentation without endangering anyone. To judge whether the treatment has effected a cure, unwrap the cloth and grip the pipe firmly in the hand. If the heat rapidly gives way to a deathly cold, you still have some more latent heat to deal with; if it remains no more than chilly, you may proceed further towards the eaves. Like all the best clinical signs this requires experience—say 25 feet of one-inch pipe de-iced successfully qualifies for consultant rank.

* * *

Following reverently in the footsteps of the Continental masters we have started to diagnose *dermatoses invisibles.* As we grow more expert we pay less attention to the crudely perceptible components of any eruption and concentrate on the (to the uninitiated) normal parts of the skin. This puzzles our patients and our colleagues, and it certainly produces some startling diagnoses. Our efforts have not passed unnoticed, for the other day we were visited by *un homme invisible*, a pleasant fellow who spoke slowly and indistinctly, for he has *une voix inaudible.* We gathered enough to realise that a biopsy was essential and this was duly done. The slide came back this morning. We must confess that there is nothing to be seen on it macroscopically or microscopically. This result has caused some perplexity in the department. One school declares frankly and scornfully that we removed an adjoining fragment of the ether in error; another more kindly believes that the invisibility of the section is corroborative evidence that the right piece was excised; while a third suggests that our pathology department have risen to the occasion and used *une teinture invisible* to stain it. We hope to have all this sorted out by next week because our patient has promised to bring up *une amie invisible* who has a *dermatose visible*, which he says spoils her appearance (or does he mean her non-appearance?).

* * * *

I suppose all of us, even peripatetic correspondents, talk shop in front of our children. But it came as a mild surprise when my five-year-old returned from Sunday school proudly bearing a coloured portrait which he had executed, and which he assured us was a likeness of John the Dentist.

* * *

This evening, browsing through *The Lancet* of Dec. 22, 1951, I read the Peripatetic's account of a viva held in the General Election season, and of how he took one specimen over to the light for inspection, "like a customer matching material." This reminded me of a viva here in South Africa, when one of my class-mates was being questioned by Sir Heneage Ogilvie, who had kindly come from England to examine us. Among other specimens, my friend was handed a segment of the sciatic nerve for comment. Somewhat nonplussed, he turned it this way and that, just like a customer who cannot make up her mind which of two materials to choose. After a suitable pause the examiner raised a patient eyebrow and asked, "Well?" At this my poor colleague delivered his considered verdict. "Well, sir," he said, "I think it is a piece of asparagus." He did not tell me Sir Heneage's reply.

* * *

The Minister may like to hear how one of his hospitals is cutting down the cost of its ambulance service. Here is the note I received when I sent them a case:

> Dear Doctor,—Your patient X. Y. Jones has now been admitted under the car of Professor Smith.
>
> Yours faithfully,
>
> Z. Y. Robinson,
> First Clinical Assistant.

Letters to the Editor

DRUG RESISTANCE OF MICRO-ORGANISMS

SIR,—Your leading article of March 15 says that, for staphylococcal infections outside hospitals, penicillin remains the most active chemotherapeutic agent. There is, however, evidence that penicillin-resistant strains of *Staphylococcus pyogenes* are increasing outside hospital.

The number of cases of impetigo referred to the skin outpatient department of the Royal Infirmary, Sheffield, has increased in the last three years as follows:

1949 ..	.. 171 cases of impetigo	(4457 new patients)
1950 ..	.. 202 " "	(4682 " ")
1951 ..	.. 294 " "	(4462 " ")

The great majority have been referred because penicillin ointment has proved valueless. Of the 294 cases seen in 1951, 63 were investigated bacteriologically. *Staph. pyogenes* was cultured in all, and in 48 (77%) the strain was penicillin resistant. Obviously there has been some selection, since only those cases which do not respond to penicillin are likely to be referred to hospital; but, nevertheless, the reappearance of large numbers of cases of impetigo, particularly in children, after its virtual disappearance suggests that penicillin-resistant strains of staphylococci have increased amongst the general public.

Chloramphenicol applied locally in the form of a cream (250 mg. in 1oz. 'Lanette wax' base) has been used during the last eighteen months for the penicillin-resistant infections in impetigo. The cream works as dramatically as penicillin did when it was first introduced, and recovery from severe bullous impetigo in 5–7 days is common.

One patient only has developed contact dermatitis during the treatment of impetigo. The dermatitis appeared within a few hours of the first application of the chloramphenicol cream, but patch tests to the chloramphenicol base and cream, carried out a few days later, were negative. Several patients whose varicose ulcers have been treated with the cream over a period of several weeks have developed dermatitis around the ulcers. It is therefore probable that, as with penicillin, more widespread use of chloramphenicol locally will reveal that it is not as innocuous as it first seems.

Whether it is justifiable to use such a valuable antibiotic locally for skin infections and wounds which do not endanger life is debatable. There is, however, a great temptation to use a treatment which will cure one's patients at the present time, and to forget the possibility of producing resistant organisms for the future. Dr. Banks's remarks encourage us to hope that chloramphenicol-resistant strains of *Staph. pyogenes* will not appear as quickly as did penicillin-resistant strains.

Rupert Hallam Department of
Dermatology,
Royal Infirmary, Sheffield.

I. B. SNEDDON.

SIR,—I have read with interest Dr. Stanley Banks's letter of March 15. There is no doubt that the number of patients with penicillin-resistant staphylococcal infections is on the increase; and the question of their treatment is very important.

Dr. Banks states that until recently he used aureomycin in penicillin-resistant staphylococcal cases, with excellent results except for the side-effects of nausea and diarrhœa. In some female patients the side-effects were such that treatment had to be stopped by the third day. This experience led him to try chloramphenicol, and his results with this drug have been good.

He notes that practically identical zones of inhibition by chloramphenicol and aureomycin continue to be obtained in all recent strains of *Staphylococcus pyogenes* examined at the Park Hospital.

He concludes that the drug of choice in penicillin-resistant staphylococcal infections is not aureomycin but chloramphenicol, because "the latter is effective, is available, is cheaper, and causes less nausea and diarrhœa."

For the same reasons I would say that the drug choice in penicillin-resistant staphylococcal infections aureomycin:

1. The effectiveness of aureomycin in penicillin-resis staphylococcal infections is well established.

2. Aureomycin is freely available for the treatment penicillin-resistant infections.

3. As the effective dosage of aureomycin is considerably smaller than that of chloramphenicol, the cost of treatm with aureomycin is less. Many clinicians have been u too high a dosage of aureomycin; it has been found that h the previous recommended dosage of 25 mg. per kg. body weight is effective in most infections.[1,2]

4. Nausea, vomiting, and gastro-intestinal disturbanc were more common with earlier preparations of aureomyc These side-effects have progressively diminished as improve methods for higher purification of the antibiotic have b developed. Aureomycin crystalline hydrochloride, as no produced in England, rarely produces side-effects. I susceptible patients the administration of gr. 5 sodiu bicarbonate with each capsule is of value.

Basu[2] has recently reported that no untoward o toxic effects resulted from protracted treatment of number of patients with aureomycin in the smalle dosage (i.e., one 250 mg. capsule every 6 hours), and th therapeutic response was excellent.

Lederle Laboratories Division,
Cyanamid Products Ltd.,
London, W.C.2.

A. T. MENNIE.

THE UNESTABLISHED PRACTITIONER

SIR,—Dr. Russell, in his letter last week, criticis the B.M.A. on three counts. Firstly, that the Association has consistently refused to support any betterment of the conditions of assistants and the small-l doctor, and has sponsored no plan to encourage partnership practice; secondly, that in spite of this the Association claims to represent "adequately" the unestablishe practitioner; thirdly, that there is not one assista or unestablished practitioner on the Working Part set up to make recommendations on the distributio of the Central Professional Pool.

Since these criticisms have been openly made in th correspondence columns of your journal, it is only rig that your readers should be made aware of the facts.

On Dr. Russell's first point, the General Medic Services Committee in November, 1949, already antici pating the wishes of assistants and unestablished pra titioners, invited a number of doctors—representati of these classes—to join a small subcommittee to stud current problems. This purely ad-hoc arrangeme was superseded in November, 1950, by a further Su committee drawn from personnel selected from a wi field, pending the establishment of the more detai machinery necessary to set up a permanent Subcommitte elected on democratic lines. These two Subcommitte drew up a charter for assistants which now appears the Association's handbook.

Now for the charge that the Association does t adequately represent the young practitioner. La year the G.M.S. Committee set up an Assistants a Young Practitioners Subcommittee to represent t interests of assistants and young doctors wishing t enter general practice or not yet established in it. Th subcommittee is now fully representative: an elector roll of all assistants and unestablished practitioners h been compiled, the country divided into six areas, a in each area the assistants and unestablished princip each elect one member. In addition to these twelve, t Subcommittee includes four members of the G.M. Committee. The Subcommittee has elected two repre sentatives to the G.M.S. Committee.

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1. Wright, L. T., Schreiber, H., Metzger, W. I., Parker, J. *Surg. Gynec. Obstet.* 1951, 94, 661. Flippin, H. F., Matte W. V., Schimmel, N. H., Boger, W. P. *J. Amer. med. A* 1951, 147, 918. Douglas, R. G. *Med. Rec. Ann.* 1951, 45,
2. Basu, A. K. *Lancet*, 1951, ii, 909.

Dr. Russell is correct in saying that the Working ty does not include an unestablished practitioner. the other hand, the views of the Subcommittee e been fully expressed to the Working Party, and continue to be as and when required.

he G.M.S. Committee has gone to considerable uble in establishing a democratically elected Submmittee to represent assistants and young practiners, and your readers may well wonder on what unds the "Unestablished Practitioners' Group" genuinely claim to represent the unestablished ctitioner.

F. GRAY

avistock House,
London, W.C.1.

Chairman, Assistants and Young
Practitioners Subcommittee.

JECTION ROUTINE IN OPERATING-THEATRES

SIR,—We have read with interest the article (Feb. 23) General Dimond, Miss Pollard, and Mr. Adamson, der the above title, and agree that many of their ggestions would help to reduce the risk of accidental ninistration of noxious substances.

There is one proposal, however, with which we must agree as a result of recent tests. This is 13(*b*) which tes: "All non-injectable fluids used for storage ampoules and syringes should have a distinctive colour. y contamination of the contents of a cracked ampoule ld then be seen." This practice is fairly widespread operating-theatres although it has been condemned Macintosh.[1]

Since finding a cracked ampoule that had been stored a coloured solution and which had not acquired any our, we have carried out several tests to ascertain ether in fact sufficient colour can be absorbed from ed antiseptic solutions to make detection of conmination certain:

antitative Chemical Tests

Twelve imperfectly sealed or very slightly cracked ampoules distilled water were placed in a solution containing 1 in 40 liquefied phenol coloured with about 1 in 600,000 of sin, and were kept in this solution for four days at om-temperature.

At the end of that time they were removed and examined. l were covered with a faint pink coating which made the ntents appear pink until the ampoule was thoroughly aned with a cloth. Two of the ampoules were so badly acked that they came to pieces and were discarded. Three owed sufficient pink colour for it to be quite obvious that ey were contaminated. One of the remaining seven showed very slight trace of pink at the meniscus when carefully amined at a certain angle only. The other six were cometely water-white, and three observers could not see any ace of pink colour. These last seven ampoules were tested ith ferric chloride solution and bromine water with the llowing results: (1) using the ferric chloride test, three npoules gave a strongly positive reaction, one a weakly ositive reaction, and three a negative reaction; (2) using e bromine water test, five ampoules gave a strongly positive sult, one a weakly positive result, and one a negative result.

uantitative Chemical Tests

(*A*) Six ampoules, three containing 10 ml. and three 20 ml. distilled water, were slightly cracked and were stored in loured phenol solution as in the tests described above.

When removed they were all coated with pink dye, but on reful washing and vigorous wiping with a clean cloth no ink colour remained. (It must be emphasised that the ink dye adheres persistently to the outside of the ampoules, nd, unless they are carefully washed, this film could be istaken for a coloured solution.)

10 ml. quantities of the fluid from the 20 ml. ampoules and ml. quantities from the 10 ml. ampoules were assayed for henol by the method of the *British Pharmacopœia*. The mount of phenol in 10 ml. of solution was as follows: 9·3 mg., 8·3 mg., 11·3 mg., 22·2 mg., 19·4 mg., and 32·8 mg.

(*B*) It was then suggested that these tests should be epeated under operating-theatre conditions. Twelve mpoules of saline were slightly cracked and allowed to stand n coloured 1-in-40 phenol solution for one week. The container was moved about in the theatre by the staff each day. The period of one week was chosen since this seems to be an average time for ampoules to remain in an antiseptic solution.

At the end of this time five ampoules were so badly damaged that their contents were obviously contaminated. Of the remaining seven, that with the smallest crack was colourless, and a test with bromine water was strongly positive. The remaining six, which showed no colour change, were assayed by the *British Pharmacopœia* method. The amount of phenol in 10 ml. of solution in these ampoules was as follows: 35 mg., 48 mg., 92 mg., 19 mg., 25 mg., and 26 mg.

To determine how much coloured phenol solution could be added to a colourless ampoule before the addition became detectable, quantities of coloured phenol solution were added from a micro-burette to 20 ml. ampoules of water. When 1·75 ml. was added it was impossible to detect any colour. With 2·0 ml. it was just possible to perceive a faint pink colour when looking at a white background through the depth of the ampoule. Several observers examined the latter ampoules and were unable to detect colour in the solutions. In artificial light it became almost impossible to notice colour in any ampoule. 2 ml. of 1-in-40 phenol solution represents 50 mg. of liquefied phenol.

It was also suggested that the use of blue colour might make detection more certain; therefore the quantitative tests were repeated, using 1 in 600,000 of methylene-blue. Each of four ampoules tested showed a slight trace of blue colour at the meniscus when very carefully examined at certain angles; but the colour was certainly not sufficient to render contamination obvious. When tested with bromine water the ampoules gave a strongly positive result.

Further tests were carried out with more deeply coloured solutions of phenol. It was found that the depth of colour of the storage solution had to be such that the ampoules themselves were invisible in the solution before the contents of each cracked ampoule became coloured.

These experiments show that appreciable quantities of phenol may pass into cracked ampoules even if the crack is exceedingly small; but, except when the phenol solutions are very deeply coloured or the ampoules are grossly cracked, the contamination may not be obvious. We suggest, therefore, that other methods should be sought.

R. W. COPE
F. PRESCOTT
T. D. WHITTET.

London.

MEDICINE WITHIN THE ATLANTIC COMMUNITY

SIR,—Whilst agreeing in essence with Dr. Meiklejohn's second article (Feb. 16), I feel that the arrangements for young British doctors to work in American hospitals are rather better than he suggests.

I am at present working in Canada under an exchange fellowship of the British Empire Cancer Campaign, and recently was able to pay a very brief visit to a few of the hospitals in New York, Philadelphia, and Boston. In the course of less than two weeks I met no fewer than five British doctors and heard talk of three others; two are in receipt of fellowships, three are working as junior interns, and two have recently come to settle on this side of the Atlantic. This is a better "haul" than the three young British doctors whom Dr. Meiklejohn met during his three months' travel through the U.S.A.; and I would emphasise that I was not attempting to contact my fellow-countrymen.

In Canada it is equally possible for postgraduate students from Britain to work in hospitals, and the resident staff here includes at least five doctors from the "Old Country" who are widening their experience. Others are working elsewhere in the city and, I understand, throughout Canada.

I do not wish to detract in any way from the most valuable and illuminating analysis of medicine across the Atlantic which Dr. Meiklejohn has given us; but lest others should be discouraged from attempting to cross the seemingly unbridgeable ocean, I think it worth recording my small experience.

Toronto General Hospital,
Ontario, Canada.

R. J. DICKSON.

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[1] Macintosh, R. R. Lumbar Puncture and Spinal Analgesia. Edinburgh, 1951; p. 142.

AN UNUSUAL EPIDEMIC

SIR,—In our capacities as otologist (G. M.) and general practitioners (R. C. and H. W.) we have in recent weeks seen 13 cases similar to those described under this heading by correspondents.

In all these cases the onset, the cardinal symptoms, and the duration of the illness were much alike.

The patients usually presented themselves with the complaint of suddenly feeling dizzy while going about their ordinary business. The degree of dizziness varied; but the first attack was always the worst and in some cases caused the victims either to sit down or to vomit, or both. The attacks usually lasted less than an hour, but in 2 cases they lasted 6–7 hours. Only 1 patient admitted that during the attack objects seemed to be rotating round her; and even in this case the history did not suggest true labyrinthine disturbance. Palpitation was almost invariably reported, and usually there was a feeling of precordial oppression. The patients also had vague digestive disturbances often with a complaint of "wind"; vomiting was confined, with 1 exception, to the younger patients, but nausea was a constant symptom. There were periods of remission, during which the patients were quite well; and relapses were common.

A peculiar "acetylene" odour was discernible in the patients' breath; and sometimes, especially in the younger patients, this rapidly permeated the atmosphere. The stools were always pale, but pathological examination was negative.

In the central nervous system no abnormal signs were found. There was no disturbance of sight or hearing, nor was there any tinnitus; the tympanic membranes were normal. At no time was nystagmus observed. (Two patients were doctors' wives, and two were medical practitioners; and we feel that such a disturbance, even if transitory, would have been noted.) There was no rombergism, incoördination, or past-pointing. The blood-pressure was within normal limits.

Quantitative caloric tests were done in one case—a boy, aged 12, who was still having intermittent attacks and had very distinctly the peculiar odour in the breath. These tests were negative.

In these cases it does not seem that the labyrinth itself was always involved. The condition may perhaps be due to a virus. Treatment can only be symptomatic, and fortunately complete recovery takes place in 2–3 weeks.

Lincoln. GEOFFREY MOREY.
Sleaford. ROLAND CUBITT
HOWARD WILSON.

SIR,—I have read with great interest your annotation of Feb. 9. For some years I myself have observed, and I have been interested in, a mild form of the syndrome that you describe.

Here actual falling, vomiting, and the necessity for bed rest have not occurred in the many cases I have seen. The usual complaint is a feeling of "light-headedness," perhaps with a feeling of instability. This continues for 7–10 days, improving gradually, and is not accompanied by overt objective signs. Attacks are sometimes accompanied by ill-defined malaise and mild depression, and interfere with work. The symptoms tend to be less severe in the morning, and to become progressively worse as the day goes on. On first lying down in bed at night the vertigo is worse than at any time, with a feeling of instability and rotation, like that transmitted by a ship in a moderate sea.

Kolar Gold Field,
Champion Reefs,
South India. W. B. ROANTREE.

SIR,—On March 3 I saw a hospital departmental sister who had that morning developed typical symptoms of epidemic vertigo; on examination there was no abnormality apart from slight lateral nystagmus.

The nausea and vertigo cleared up within a week, but on March 17, 14 days later, the patient developed moderately severe herpes zoster affecting the left fourth thoracic segment. Symptoms of an ordinary cold preceded the onset of vertigo, but there was no history of contact with zoster or varicella.

The development of these two conditions within 14 days may have been merely a coincidence; but since infection by a neurotropic virus has been suggested as a possible cause of epidemic vertigo, I thought this worth recording.

Pembury Hospital, Kent. R. M. MILLER.

PONGOS

SIR,—It is with a sense of shame that I read in your issue of March 15 that the gorilla is likely to become extinct within a hundred years—largely owing, no doubt, to the fact that hunters kill the parents in order to capture the young. Cannot something be done internationally, as I believe has already been done for the panda, in order to protect the gorilla?

Newport Pagnell, Buckinghamshire. A. A. CLAY.

B.M.R. AND RADIO-IODINE TESTS

SIR,—The clinician's main objection to the B.M.R. is that it is so commonly abnormal in nervous patients. Keating et al.,[1] whose results Dr. Robertson (March 8) quotes in support of his B.M.R., reported a mean B.M.R. of + 19 ± 2·8% in 30 "functional disorders" whose radio-iodine test results were strictly normal.

Radio-iodine and B.M.R. tests each measure a different aspect of thyroid function subject to different sources of error. Radio-iodine tests are only in the development phase and not yet ready for routine clinical use; but surely the clinician who can use with discrimination whichever test is the more appropriate is on firmer ground than he who uses only the B.M.R.?

Postgraduate Medical School of
London, W.12. RUSSELL FRASER.

THE TREATMENT OF PEPTIC ULCER

SIR,—I cannot agree with Dr. Doll's renewed arguments that his results would show whether or no phenobarbitone has a good effect on gastric ulcers. For me there are still three objections. The fact that in the series which Dr. Doll has studied no benefit has been demonstrated does not necessarily imply that the drug is ineffective in all cases. Any hospital series is selected compared with the patients whom the general practitioner sees. An imaginary example will show this. Let us suppose as an extreme case that 50% of gastric ulcer patients do so well with phenobarbitone that there is no need for their doctor to send them to hospital, and that the other 50% derive no benefit at all. Then Dr. Doll's trial will take place entirely on patients who derive no benefit, but the deduction that phenobarbitone is useless would be incorrect.

The second fallacy is that the possible effect of dosage is neglected. Different patients differ in their sensitivity. A standard dose may be so low as to be useless to one patient, and so high as to be harmful to another.

The third fallacy is the one which really interests me. Dr. Doll has not tested the effect of phenobarbitone on gastric ulcer patients: he has tested the interaction between phenobarbitone and a type of treatment which in theory could neutralise the effect of phenobarbitone. One way in which barbiturates are believed to act is by lessening the effect of emotional tension on the small intestine and colon. They lessen emotional small-intestinal hurry and hence they reduce colonic fermentation and irritation. This is important because irritation of the colon reflexly lowers gastric tone and gastric ulcers heal badly unless the stomach empties properly and contracts. Dr. Doll's dietetic and alkali régime favours the stomach but in some patients undoubtedly produces colonic fermentation which phenobarbitone is powerless to prevent. I think that this is probably why Dr. Doll gets better results in certain patients with bed treatment. If gastric tone is inhibited, the stomach stretches less with the patient lying supine. Conversely, if I am unable to improve gastric tone in my patients, I feel compelled to recommend bed treatment, even though for long-term

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1. Keating, F. R., Haines, S. F., Power, M. H., Williams, M. M. D. *J. clin. Endocrinol.* 1950, 10, 1425.

ons I consider it a mistake to bring ulcer patients hospitals except for surgery, or of course for rgencies.

ndon Hospital, E.1. **DENYS JENNINGS.**

R.—Dr. Avery Jones has nodded. In his letter of ch 15 he misquotes me, and the English version of hartz which he gives is a travesty of Lenhartz: hartz started feeding within two to three hours of a re hæmorrhage and gave 2–3 eggs on the first day. calorie value of his diet rapidly rose to 1588 calories he seventh day and 2500 on the tenth. After studying is Carroll Dr. Avery Jones describes this as a starva- régime which "does not provide basic calorie irements before the tenth day."

his is the point which I tried to make. In the latter of the 19th century a bad treatment—starvation— laced the better treatment of feeding. At the turn he century a number of excellent clinicians made the nt which Dr. Avery Jones makes: more patients were ng from starvation than from hæmorrhage. But pite numerous well-documented papers the bad form reatment continued. We, in our turn, cannot afford e complacent. There is always a chance that theorists l persuade us into following a retrograde course of ion. It seems to be a law of medicine that the doctors h few patients have plenty of time to write; and the tors with many patients are averse from generalisation.

ondon Hospital, E.1. **J. E. RICHARDSON.**

HYSTEROSALPINGOGRAPHY IN FEMALE INFERTILITY

IR,—The correspondence under the above heading been most interesting. Dr. Pygott (March 1) will be erested to know that the radiation dosages quoted Dr. Preiskel and Dr. Pollock (Feb. 16) were measured this hospital, and refer to doses to the ovary.

ver a series of 14 unselected hysterosalpingography aminations, the average dose due to screening was 20 r, d that due to radiography 7 r. The highest *skin* dose orded in this series was 80 r, corresponding to 4½ minutes' eening and three radiographs, giving an estimated ovary se of 55 r. According to Glucksmann,[1] this dose is one-third that required to induce temporary sterility.

Unfortunately, the inverse square law does greatly fect the dosage to the patient.[2] For two exposures at fferent focal distances giving the same film-blackening nd therefore approximately the same radiation dose the film) the dose at any fixed point in front of the m will be greater for the shorter focal distance. Hence e advantage of using a long focal distance. Hultberg al.[3] have recorded some dire consequences of short- istance radiography.

Being a physicist, Sir, I will not comment on the vantages of screening in hysterosalpingography, cept to say that many radiologists manage without it. eing no geneticist, I would hesitate to assert that 27 r the ovaries produces any serious result. I would draw our attention, however, to a recent meeting of the ritish Institute of Radiology at which the possible fects of diagnostic X-radiation over a whole population ere considered, particularly the genetic effects.[4] Among e facts presented was the following:

> About one patient in 500 in the X-ray department of this ospital undergoes hysterosalpingography, and yet (even with non-screening technique) over one-third of all the radiation iven to the reproductive organs of female patients is adminis- ered in these examinations, and two-thirds if a screening echnique is employed. Further, hysterosalpingography is lmost always performed on women anxious to bear children, ot on post-menopausal women, where the dose would matter r less. For comparison, may I mention that for each postero-anterior chest radiograph the ovaries receive about 0·001 r.

Most geneticists agree on the need for giving the smallest possible quantity of radiation to the gonads of those who will subsequently reproduce.

University College Hospital,
London, W.C.1. **S. B. OSBORN.**

Glucksmann, A. *Brit. J. Radiol.* 1947, suppl. no. 1, p. 103.
Martin, J. H. *Ibid*, 1947, 20, 279.
Hultberg, S., Larsson, L. E., Eklund, L. *Acta radiol., Stockh.* 1950, 33, 376.
Brit. J. Radiol. (in the press).

ANÆSTHESIA FOR TUBERCULOUS PATIENTS

SIR,—I have read with great interest Dr. Mushin's letter of March 22. I have not found tuberculous patients to suffer from the use of the standard inhalation drugs and techniques, and I try to resist the temptation to give them "something different." However, these patients commonly recite with great conviction the anæsthetic advice of their physicians, who may condemn inhalation anæsthesia. In these circumstances, although the physician may have no anæsthetic experience, it is unwise to overlook the patients' beliefs completely, otherwise any postoperative reactivation of disease may be attributed to the anæsthetic. Some physicians and their patients then must be re-educated before the anæsthetist may choose freely the anæsthetic of his choice.

London, E.C.1. **ROBERT I. W. BALLANTINE.**

SIR,—Dr. Mushin raises an important issue in his letter last week.

May I plead for the wider use of intravenous procaine? In a concentration of 0·5% combined with nitrous-oxide/oxygen and a relaxant I have used it over the past two years for a wide variety of cases, and believe it to be superior to many more popular but more toxic drugs. It is rapidly detoxicated and excreted, has a beneficial effect on the heart and circulation, and is a potent general analgesic and a broncho-dilator. It does not produce respiratory depression, nor, contrary to general belief, does *it* appreciably reduce blood-pressure or increase hæmorrhage. In good-risk cases it may be given in a dosage of 5 g. over 2–3 hours without ill effect. Its use in a slow continuous drip during the postoperative period is also beneficial, since it gives sedation without morphine, and postoperative respiratory complications appear to be reduced.

In my opinion it could be more widely adopted in anæsthetic practice, particularly in the type of case described by Dr. Mushin.

London, W.1. **R. BLAIR GOULD.**

TREATMENT OF SCARLET FEVER

SIR,—This January, as in the previous winter, I went to London to study progress in medicine. The two daughters, 6 and 8 years old, of one of my Danish friends living in London got severe scarlet fever. The doctor, a specialist in pædiatrics, thought that penicillin was useless; but, much against his will, he gave the children a few injections of it. On his instructions all the linen was disinfected; bottled milk was forbidden; and the sending of letters was not allowed. The children were kept in bed for 2 weeks, isolated in their rooms for 3 weeks, and not allowed to go to school for 5 weeks. What trouble and expense, and what unnecessary risk of complications!

Several years ago T. Jersild,[1] of Copenhagen, in a report on penicillin therapy in scarlet fever and complicating otitis, showed that 90,000–150,000 units twice a day will rid the nose and throat of hæmolytic streptococci within 48 hours. To prevent the reappearance of streptococci the penicillin therapy should be continued for 6 days. The average febrile period was only 4–5 days, and no complications developed; the average stay in hospital was only 8 days. Since then more than six thousand patients with scarlet fever have been treated by this method in the department of epidemiology, Blegdamshospital (Prof. H. C. A. Lassen). The results have been just as favourable in the later cases as in the earlier ones. Home treatment with isolation for only a few days is now very common in Denmark. No disinfection is applied. The children are sent back to school as soon as possible—generally 8–10 days from the start of treatment. Complications have completely disappeared.

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[1] *Lancet*, 1948, i, 671.

Perhaps it would be a good idea for some English doctors to visit Denmark to see for themselves how easy, cheap, and safe the treatment of scarlet fever can be.

Blegdamshospital,
Copenhagen.
N. B. KRARUP.

REPAIR OF INGUINAL HERNIÆ

SIR,—None of the many methods for repairing inguinal herniæ seems to include any technique for strengthening the posterior edge of the inguinal ligament. In suitable cases I have found the following technique useful.

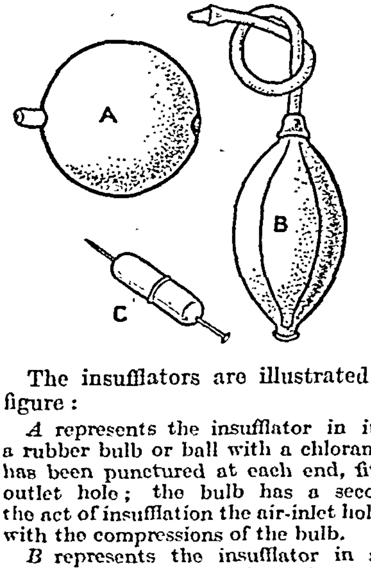
A stout piece of 'Nylon' or silk is laid between the pubis and the outer attachment of the inguinal ligament. When the sac of the hernia has been dealt with and any form of repair is being carried out, this length of suture material is used to strengthen the hold of the sutures between the conjoint tendon and the inguinal ligament, by passing the needle round the length of material and the free edge of the inguinal ligament. This procedure is similar to that used by a tailor when he sews a buttonhole.

I have followed this simple procedure many times; and I am sure that it is a harmless method of preventing the back of the inguinal ligament from becoming frayed during the repair.

Edgware General Hospital,
Middlesex.
D. B. CRAIG.

CHLORAMPHENICOL INSUFFLATOR

SIR,—When I recorded local chloramphenicol treatment for chronic otorrhœa last year,[1] I mentioned the method of insufflation of the powder. Two simple insufflators were designed for insufflating chloramphenicol powder directly from its capsule, for the local treatment of "safe" chronic otorrhœa and for the prevention of sepsis in the healing of fenestration and mastoid cavities. Several colleagues have found these insufflators very effective in treating chronic suppurative otitis media and infected or potentially infected wounds.



The insufflators are illustrated in the accompanying figure:

A represents the insufflator in its simplest form. It is a rubber bulb or ball with a chloramphenicol capsule, which has been punctured at each end, fitted closely into an air-outlet hole; the bulb has a second (air-inlet) hole. In the act of insufflation the air-inlet hole is closed synchronously with the compressions of the bulb.

B represents the insufflator in slightly more elaborate form. It has an air-inlet valve and rubber tubing, which can be adjusted at an angle. Several colleagues, however, prefer the rubber bulb with air-inlet valve, but without the attached tubing.

C represents the capsule, pierced by means of a large pin; a hat-pin is very suitable for this purpose.

The insufflator has the advantages of simplicity, cheapness, absence of fragility, economy of material and time, and convenience. One capsule should suffice for several treatments. The air entry through the inlet hole (*A*) is so free that the suck-back of powder into the bulb is insignificant. Nor does there appear to be any extensive suck-back of powder when bulb is fitted with an efficient inlet-valve, as in *B*.

Repeated use of chloramphenicol powder may give rise to local allergic reactions; and, if one uses the method of insufflation often, it is probably advisable to avoid inhaling the powder lest such a reaction should develop in the respiratory tract.

Many other therapeutic agents in powder form can be insufflated in this way from transparent gelatin capsules, which can be easily obtained and filled. Starch powder 'K285' (Boots) is very light, and dry, and is an excellent diluent to mix with coarser powders for easy insufflation.

London, W.1.
W. H. B. MAGAURAN.

PROCTALGIA FUGAX

SIR,—Sir Henry Tidy (Feb. 9) and Sir Adolphe Abrahams (Feb. 23) state that proctalgia fugax is rarely mentioned in textbooks, but I have found that the literature of this condition is fairly extensive, though scattered.

As Sir Adolphe points out, the first definite account seems to be that by MacLennan,[1] in 1917, but Curling[2] in 1871 described a somewhat similar condition. Nothnagel,[3] discussing proctospasm, gave "hysteria and very advanced degrees of neurasthenia" as two of its causes. Gant[4] stated that the intermittent pain of *phantom* stricture of the rectum was caused either by rectal valves or by spasmodic contractions of the levator ani or sphincter muscles.

Ryle[5] regarded the condition as a visceral neurosis and thought that some patients could be relieved by inflating the rectum with air. A correspondent[6] who suffered attacks for 25 years, attributed them to a "chill" after discarding his heavy underwear in cold weather. McEwan[7] had a patient whose attacks stopped when he joined the Army, but returned with extreme severity and frequency when he was discharged. Smith[8] reported on a patient whose attacks could be aborted by assuming a doubled-up squatting posture. A correspondent[9] cited the case of a highly strung barrister who had an attack whenever he rose to plead in court. Beckman[10] met a colleague whose attacks invariably stopped when he gave up smoking. Carlill[11] saw a girl whose rectal symptoms were associated with *petit mal.* Bolen[12] examined a patient during an attack and described spasm and hyperæmia in the rectum. He compared the condition to certain types of pseudo-angina. Pruitt[13] thought that fatigue and emotional stress may be predisposing factors. Rosser[14] suggested that an intussusception of the sigmoid colon into the rectum may be the cause.

I have myself seen many cases, and I pointed out[15] that proctalgia fugax may be the sole physical manifestation of a psychoneurosis, or it may be associated with other physical manifestations of a disturbed emotional state. There is little difference, except in the viscus concerned, between proctalgia fugax, "gastralgia," "enteralgia," "colalgia" (as described by the earlier sicians), globus hystericus, spastic colitis, pseudo-ina, many attacks of asthma and dysmenorrhœa, and ay other psychosomatic conditions.

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[1] *Lancet*, 1951, ii, 178.

1. MacLennan, A. *Glasg. med. J.* 1917, 3, 88.
2. Curling, T. B. *Syst. Med.* 1871, 3, 163.
3. Nothnagel, C. W. H. Diseases of the Intestines and Peritoneum. Philadelphia, 1904.
4. Gant, S. G. Constipation and Intestinal Obstruction. Philadelphia, 1909; p. 199.
5. Ryle, J. A. *Lancet*, 1935, ii, 343.
6. *Ibid*, p. 404.
7. McEwan, P. *Ibid*, p. 580.
8. Smith, R. N. C. *Ibid*, p. 581.
9. *Ibid*, p. 581.
10. Beckman, H. *Ibid*, p. 634.
11. Carlill, H. *Ibid*, p. 472.
12. Bolen, H. L. *New Engl. J. Med.* 1943, 228, 564.
13. Pruitt, M. C. *Sth. med. J.* 1944, 37, 442.
14. Rosser, C. *Ibid*, cited in discussion.
15. Murray, J. B. Some Common Psychosomatic Manifestations. London, 1951; p. 138.

he description of proctalgia fugax given by the ient is constant and is limited only by his vocabulary; there can be little doubt about the diagnosis. He uld be assured that there is no serious cause for his nplaint, because he often fears that his condition is to a mortal disease. He should be told that his nptoms arise from an emotional state, that he must ept them in spite of their alarming nature, that ysical treatment will only precipitate them, and that itemplation and expectation of the attacks will voke them. The physician giving this advice to an ablished sufferer, who has gained no permanent ief from all sorts of physical remedies, can be quite e that he will go elsewhere for his treatment, unless is a person of unusual intelligence and insight.

ondon, W.1. J. BARRIE MURRAY.

CAT-SCRATCH FEVER

SIR,—Professor Bedson has opened up considerably e field of discussion of cat-scratch fever by his letter March 8. The point which I desired to make in my n letter (March 1) was that the skin test may be sitive in other conditions. Professor Mollaret and his lleagues[1] have stated that the complement-fixation st is a group reaction.

As regards the evidence concerning the statement that n-specific urethritis is *believed* to be a member of the mphogranuloma-venereum/psittacosis group of viruses, dies similar to those described in the members of this tablished group[2] have for some years been reported as ving been found in urethral scrapings from some ses of non-gonococcal urethritis.[3] These disappear uring treatment with the antibiotics given orally, ari passu with the discharge, and may usually be found the relapsing case; and some believe them to be the ause of the condition.

On the other hand it must be admitted that the "virus" f non-specific urethritis has not so far been definitely stablished in animals or eggs, and there are some ifferences in the antibiotic sensitivity between these ases of non-specific urethritis and the established members of the lymphogranuloma-venereum group—notably is regards penicillin and streptomycin.

With regard to cross-reactions in skin and complement-ixation tests between non-specific urethritis and lymphogranuloma venereum it is appreciated that Professor Bedson found no association in 25 cases.[4] At the time of writing in Thailand, the bulk of my material and references are not available to me. However, without making any premature statements of opinion, I can definitely say that my own findings are not as completely negative as those of Professor Bedson. The data will, of course, be published in due course.

Bangkok, Thailand. R. R. WILLCOX.

SIR,—I fear that your annotation of Feb. 9 gives me more credit than I deserve. The first antigen made from purulent material from a clinically classical case, with transmission by a cat, was prepared by Dr. Harry Rose, of New York, from material taken from an axillary node of Dr. Franklin M. Hanger, hitherto better known as author of a cephalin flocculation test. It was another instance in which tularæmia was brought into question. I laid that ghost, but inquired about a cat contact and told Dr. Hanger what little I knew about cat-scratch fever and that his consultants' interest should be deflected from rabbits to cats. He promptly sent me some of the prepared antigen, to which he himself had reacted, and I was able to identify his infection with those of some of my former cat contact cases, and with a good many new ones as time went on.

This disease is indeed ubiquitous in this country. By intradermal-test responses against cat contacts and clinical histories and courses, its presence is now verified across our country from Altantic to Pacific, and in border states from Canada to Mexico. The cat contact still is a constant feature in American cases, though I am aware that this is apparently not true in France.

College of Medicine,
University of Cincinnati,
U.S.A. LEE FOSHAY.

ECONOMY IN HOSPITALS

SIR,—I should like to comment on two points in your leading article of March 1:

1. You plead for a more rapid turnover of cases. Most hospitals are already doing their utmost in this direction. The speed can only be increased by greater provision for convalescent patients, particularly those who cannot look after themselves completely. I refer especially to post-operative "pinnings" of fractured femoral necks and similar cases.

2. You refer to travelling expenses of part-time consultants, and also to payment for time spent in travelling. In the first place the travel allowance does not now cover the cost of journeys. Secondly, in the provinces a very large number of surgeons are doing clinics and operating sessions which considerably exceed the notional half-day of $3^1/_2$ hours, and then spend up to an hour travelling to another hospital or to their home. These consultants are not being paid for all the work they are doing, let alone for the time they spend travelling. To add to their difficulties many of them are shortly to be deprived of the assistance of their registrars.

Bexhill-on-Sea,
Sussex. E. W. BINTCLIFFE.

MASS TECHNIQUES

SIR,—I was interested in Dr. Burn's suggestion (March 15) that mass radiography should be combined with "some form of health check-up." I have already developed this theme[1 2]; and I wrote:

> "Mass Radiography is part of a revolutionary development in medicine, the implications of which are not yet recognised. We are at the beginning of a new medical era—the era of Presymptomatic Diagnosis, in which treatment will begin before the patient feels ill, and, if the disease is infectious, before he becomes a danger to others. Today, symptoms select the sick and bring them to the clinic. Tomorrow, the doctor will seek actively for disease among the apparently healthy. At present we deny to our fellow men the routine inspection the engineer gives to our machines. Men, as much as aeroplanes and motor cars, need periodic scrutiny and maintenance overhauls."[2]

Are periodic health examinations for all a pipe-dream or a practical possibility? Our hands are full dealing with the sick; surgeries are overflowing, clinics crowded, X-ray departments overburdened, laboratories overworked. Doctors are short of time, the health service is short of money and staff. Ffrangcon Roberts has emphasised that the demand for X-ray examinations and special investigations is rising year by year, and warns us to call a halt or face bankruptcy. If it costs hundreds of millions just to deal with the sick, how can we possibly commence periodic health examinations in the foreseeable future? I wrote that "tomorrow the doctor will seek actively for disease among the apparently healthy." How can this be done?—for the sick are few while the apparently healthy are legion.

The answer is that presymptomatic diagnosis will use mass techniques which together will form what I shall call mass medicine. Mass medicine will use streamlined techniques of established procedures. Abnormalities discovered by mass diagnostic units become the concern of individual medicine. Medicine must undergo its own industrial revolution, and the methods of the production engineer must be copied if we are to develop cheap and labour-saving methods of serving large numbers of people. Those who are sick, or think they are sick, will remain the concern of individual medicine; mass methods will only be suitable for the apparently healthy. Mass radiography is the first example of a mass technique.

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[1] Mollaret, P., Reilly, J., Bastin, R., Tournier, P. *Pr. méd.* 1951, 59, 681.
[2] Thygeson, P. *Amer. J. Ophthal.* 1951, 34, 7.
[3] Harkness, A. H. Non-gonococcal Ure 0. Durel, P., Borel, L. *Bull. Soc. franç.* 14. Coutts, W. E., Vargas-Zalazar, R., S er. 1951, 55, 148. Harrison, L. W., Worm is. 1939, 15, 237. Willcox, R. R. *Prac*
[4] Bedson, S. P. *Brit. J. vener. Dis.* 1950, 26, 177.

[1] *N.A.P.T. Bull.* April, 1951.
[2] *King's Coll. Hosp. Gaz.* 1951, no. 4.

White and Geschickter,[3] of Yale, have written a textbook in which they discuss a statistical approach that seems full of promise. They found that, of the 2000 recognised disease entities 200 account for virtually all the physician's consultations and most of the disability and death in the U.S.A. They have attempted to work out a method of history-taking and a diagnostic "workup" that will simply and reliably reveal these 200 diseases during health examinations. The next step, it seems to me, is to try to adapt their procedure to mass techniques.

A nurse may do a dozen Benedict's tests an hour if she boils each specimen separately. A technician could test 300 specimens an hour if he boiled them together in a water-bath. Increased production by mass methods often means a falling cost per unit produced. This, and not gross curtailment of investigations, is the solution to Ffrangcon Roberts's problem of ever-rising costs. For example, the cost of running a mass-radiography unit—say £5000 a year—is nearly all due to fixed overheads, especially staff. If we take one film, the cost per film is £5000; if we take 5000 films, the cost is £1 per film; if we take 100,000, the cost is 1*s*. per film. The graph of cost per unit falls steadily as production rises.

Other procedures that require streamlining are measurement of blood-pressure, urine testing, and hæmoglobin estimation. Simplification and adaptation for rapid repetition is what is needed.

In south-west London, since 1949, we have, along with chest radiography, made observations on heights and weights[4] and erythrocyte-sedimentation rates, and by questionaries have investigated certain social habits as modes of acquiring tuberculous infection,[5] food habits, and the incidence of major symptoms referable to body systems other than the respiratory.

A mass-radiography unit is a case-finding organisation using mass technique. Our resources have never enabled us to examine more than 10% of the population per annum, and so we have never practised indiscriminate universal radiography (the "mass radiography" of Grenville-Mathers and Trenchard[6]). We make (from chest-clinic records) spot-maps showing the place of residence of every case of pulmonary tuberculosis notified in a period of five years. Some groups of streets are found to be black spots, and here our propaganda is focused and centres arranged. Selective propaganda is used to single out those with symptoms (e.g., treating themselves at the local chemist's shop) and those living in overcrowded conditions.[7] [8]

There is room both for chest clinics and mass-radiography units to fish for tuberculosis in the pond of general practice. Dr. T. J. Lee and I, approaching the problem from the needs of a typical general practice, have found that about 5 chest films per 1000 patients per month are required. So, for a chest-clinic area of 200,000, the general practitioners will need (not necessarily ask for) 1000 films a month. I do not know a chest clinic (even those with 'Odelca' cameras) that could manage this number. As long as the general practitioner has the diagnostic facilities of a medical Robinson Crus shall continue to find many cases too late—to the na cost.

Benjamin and I[9] have shown that, if the m radiography units alone could treble their present of discovery of sputum-positive cases of tuberculos seems probable that the majority of the "unk infector pool" could be brought under medical superv in ten years—thus giving a measure of real control the infection.

Mass X-Ray Service for
South West London,
Grove Hospital, S.W.17.

F. A. NAS
Medical Dire

GAS-AIR ANALGESIA MACHINES AND TH "C.M." ATTACHMENT

SIR,—We fully agree with Prof. Chassar Moir (M 22) that nitrous oxide and oxygen is a superior anal to nitrous oxide and air. We said so, clearly. One o various machines for self-administration of gas oxygen may, as he suggests, in time replace the gas- air machines in hospitals. Our little book was wr for the general practitioner, to whom the C.M. att ment is sometimes recommended; it therefore see appropriate to discuss it.

An *initial* breath of pure gas certainly incr effective analgesia. With the C.M. attachmen position, however, the machine ceases to deliver a mixture of gas and air. Even after the bag has emptied there is a continuous additional flow of g the rate of 1 litre a minute. When we wrote our we thought that this fact was not sufficiently appreci

The capacity of the bag of the C.M. attachment to us by Messrs. A. Charles King Ltd., and m factured by the British Oxygen Company, was $2^1/_2$ l as we stated. We have confirmed this. We t Prof. Chassar Moir for explaining that the C.M. att ment was not sponsored by himself.

University College Hospital,
London, W.C.1.

W. C. W. NIXON
SHILA G. RANSOM

HICCUP DURING ANÆSTHESIA

SIR,—I have read with interest the correspond on this subject.

In a series of upper abdominal operations, inclu 20 gastrectomies, with anæsthesia by thiopent 'Flaxedil,' pethidine, hexamethonium iodide, and nit oxide and oxygen ($3^1/_2 : 1^1/_2$), using the semiclosed c absorption technique, hiccup has not occurred. patients were intubated with the largest cuffed t that would pass without trauma, were maintained apnœa by hyperventilation, were postured to red bleeding, and were conscious and in good condition their return to the ward.

It is my impression that the afferent path of the hic reflex is via the vagus, and the combined vagolytic effe of flaxedil, pethidine, and hexamethonium prevent occurrence. Dr. McGill[10] has reported a case of intracta hiccup which responded dramatically to hexamethoni

Hull.

W. N. ROLLASON

SIR,—The correspondence on this subject has brou to light a variety of prophylactic and curative measur intravenous 'Methedrine,' likely to produce a blo operation field and to be avoided in the hypertens patient; amyl nitrite, rapid but fleeting in action, ca ing transient hypotension; and deep cyclopropane an thesia, the more likely to cause cardiac irregularity w the concentration of gas is suddenly increased, a associated with increased venous oozing and respirato depression.

With pethidine to the fore as an agent for maintaini anæsthesia, I am surprised that no mention has be ade of its capacity to abolish hiccup; the small uantity required to produce this effect has no noticeable fect on the blood-pressure or respiration.

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[3] White, B. V., Geschickter, C. F. *Diagnosis in Daily Practice: an Office Routine based on the Incidence of various Diseases.* Philadelphia and London, 1951.

[4] Benjamin, B., Nash, F. A. *Tubercle*, 1951, 32, 82.

[5] Benjamin, B., Nash, F. A. *Ibid*, 1950, 31, 256.

[6] Grenville-Mathers, R., Trenchard, H. J. *Lancet*, Feb. 9, 1952, p. 319.

[7] Nash, F. A. *Ibid*, 1951, i, 689.

[8] Nash, F. A. *Ibid*, ii, 512.

[9] Benjamin, B., Nash, F. A. *Tubercle*, 1952, 33, 75.

[10] McGill, R. J. *Lancet*, 1951, i, 1018.

A convenient method is to dilute 100 mg. pethidine with yrogen-free water up to 10 ml. in a syringe of that size; us each millilitre of solution contains 10 mg. pethidine. ccording to the age and build of the patient, an intravenous ose of 2–3·5 ml. of this solution (20–35 mg. of pethidine) will variably abolish hiccup within 90 seconds, and the drug mains effective for a considerable time.

Postoperative and other forms of hiccup will also ometimes respond to this method.

St. James' Hospital,
London, S.W.12.

J. MORTON MACDONALD
Anæsthetics Registrar.

THE ETHICS OF LEUCOTOMY

SIR,—Dr. Atkin, in your issue of March 22, writes: . . . the mind always functions as a whole. A neurotic, part from his symptoms, suffers also from a faulty haracter and personality . . ." The second asseveration ontradicts the first.

Dr. Atkin, later in his letter, avers: ". . . I do not ean to pass any moral censure on the neurotic . . ." He has, in the second statement noted above, found verdict of guilty against the neurotic.

The desirability or otherwise of leucotomy, in each ndividual instance, should be assessed in terms of linical medicine, rather than by means of an affirmation of inspiration tempered by a pseudo-ethical judgment.

London, W.1.

MURDO MACKENZIE.

TERRAMYCIN IN THE PROPHYLAXIS OF OPHTHALMIA NEONATORUM

SIR,—I regret that my article (Feb. 16, p. 347) contained two errors. The strength of the eye-drops was n fact 5 mg. per ml., and of the ointment 1 mg. per g. For the ointment the makers now recommend a strength of 5 mg. per g.

Postgraduate Medical School of
London, W.12.

DONOUGH O'BRIEN.

CORSETS AND CHLOROSIS

SIR,—Your leading article last week will be of interest to the rapidly diminishing number of medical men who have seen a case of chlorosis.

You speak of it as an iron-deficiency anæmia, but is this certainly true? Chlorosis has never, for obvious reasons, been investigated by modern hæmotological methods; but Haldane and Lorrain Smith insisted that the cardinal defect was an increase of plasma—a hydræmia—rather than a deficiency of hæmoglobin in the circulating red cells: hence the importance of giving magnesium sulphate along with Blaud's pills, which was the standard treatment.

As regards the tight-corset theory it would be pertinent to ask two questions. Did the mill girl of Lancashire wear tight corsets—except on Sundays or Saturdays? They certainly had chlorosis. Did the sufferers from chlorosis abandon their tight corsets on marriage? They certainly lost their chlorosis.

Buxton.

F. ARNOT BEARN.

INTRATHECAL AUREOMYCIN IN MENINGITIS

SIR,—The views of Mr. Martinez (March 15) on intrathecal aureomycin in meningitis can be assailed both on general principle and in relation to the practical details of the cases discussed by Dr. Ainley-Walker and Dr. Bosanquet (March 1).

Mr. Martinez's belief that the infection in purulent meningitis is situated only in the vascular pia mater fails to account for the presence of living, culturable organisms in the cerebrospinal fluid (C.S.F.). He must admit that although the primary site of the infection may be in the pia mater, yet there are large numbers of organisms on the subarachnoid side of the membrane, and that there must therefore be some point in administering antibiotics by the intrathecal route provided that systemic treatment is given simultaneously. Moreover, in two of the cases to which allusion was made it seemed likely that the infection had been introduced intrathecally, and was in fact situated primarily on the C.S.F. side of the membrane. What is more reasonable, therefore, than to treat the cases with intrathecal antibiotics?

Mr. Martinez implies that systemic aureomycin might have saved the three patients who died. Yet two of them had tuberculous meningitis in addition, and the third a severe head injury—features that are overlooked in Mr. Martinez's letter. A more important point was that in the only case which recovered Dr. Ainley-Walker had found that "systemic aureomycin had failed to control the infection." It was only when aureomycin was put into the abscess cavity that the condition improved.

Department of Neurology,
Royal Infirmary, Manchester.

L. A. LIVERSEDGE.

Obituary

GEORGE WILLIAM MARSHALL FINDLAY

C.B.E., M.D., Sc.D. Edin., F.R.C.P.

Dr. G. W. M. Findlay was a man of many talents, and during his life he won distinction not only as a research-worker in tropical medicine but also as a scholar and editor.

He was born in 1893, the son of Dr. George Findlay, of Brailes, Warwickshire. From Dean Close School, Cheltenham, he went to Edinburgh University, and he was in the last year of his medical course when war broke out in 1914. He at once volunteered as medical aide in the Belgian Army, but after a few months he returned to Edinburgh to take his M.B. degree with first-class honours in 1915. He immediately joined the Royal Navy, where he served as a surgeon lieutenant till the end of the war. For these services he received the 1914 star and the médaille du Roi Albert and was appointed O.B.E.

On demobilisation he returned to Edinburgh, where he held Lister, Carnegie, and Freeland Barbour fellowships before he was appointed lecturer in pathology at Edinburgh University in 1920. He also acted as assistant pathologist to the Royal Infirmary. In 1923, with an Alice memorial fellowship, he was appointed an assistant at the Imperial Cancer Research Fund. Five years later he joined the scientific staff of the Wellcome Research Institution, where his interest in tropical virus diseases found scope. During the next years he travelled widely and visited the Pasteur Institutes in Paris and Tunis and the Rockefeller Institute in New York. But it was the problems of disease in Africa that he made specially his own. For his studies on immunisation against yellow fever in the Gambia he was promoted C.B.E. in 1935. But, alongside the observer, the synthesiser was already at work, and in 1930 the first edition of his *Recent Advances in Chemotherapy* appeared. This was accounted a bulky recruit to the series, for the first edition had over 500 pages. The third edition which is now appearing is to have four volumes, of which Findlay had finished the third shortly before his death.

During the second world war the growing importance of the African battlefields made it inevitable that Findlay should be asked for counsel and help. In the early years he visited Tunis to advise on trench fever and later Abyssinia to advise on yellow fever. In 1942 he was appointed consulting physician to the West African Forces with the rank of brigadier. Those who knew him forecast that the consequences of this appointment were bound to be evident and could not be dull. In this they were right. Doubters who believed that West Africa at war would take the sting out of him underestimated Findlay. He brought great activity to the medical work of the Force, for he had a way of generating the kind of enthusiasm which remained after he had gone. He made medical officers feel that their contribution was vital—as indeed it was—and they knew that if they ran into trouble in a good cause they could count on his backing. With Macgraith he also did a great deal to make the laboratory services contribute their full quota of basic information about the health of the troops. He himself led a team which conducted a series of interesting experiments into the spread of infective hepatitis and homologous serum jaundice.

"Findlay's first encounter with the hard facts of military medicine in West Africa was characteristic," J. W. H. relates. "He discussed a scheme for the introduction of mepacrine to suppress malaria. He was advised that his proposed dosage was not sufficient and that he should not withdraw quinine so abruptly as he proposed. He argued the matter at length with good humour and courtesy but without giving an inch. He thought that the objections to his scheme were theoretical and that the result of a trial would establish this. It was not so. Within two weeks of its being launched, Findlay's scheme was drastically amended by his own decision, and in future discussions he handsomely agreed that he had been wrong. Moreover, he even congratulated units whose medical officers had shown the good sense, as he put it, to see that they acted as controls!

"One impression persists with great clarity. How much of the literature of anything he knew. He remembered references to everything and anything; and he sometimes recalled them in great detail, quoting correctly from memory even volume and page numbers. On virus infections, particularly, there seemed to be nothing that he had not read. All this he gave freely in discussion which he was ever willing to join. He was not right about everything though he admitted few doubts to his arguments, and some perhaps took this attitude as evidence of over-confidence. But Findlay never ran away from a fact; and if he could be proved wrong he would yield with true humility—but it was hard to catch him out. We shall miss his enthusiasm and the readiness with which he could rouse the same quality in others."

Soon after his return from West Africa Findlay moved round the corner from the Wellcome Institution to B.M.A. House, where he undertook the organisation and editorship of the *Abstracts of World Medicine* and *World Surgery, Obstetrics and Gynæcology*. Here his gifts of erudition and clarity were used, but he refused to give up all contact with research and he still found time to snatch a few hours in the laboratory. Lately he had published in the *British Medical Journal* the result of some of his work on the Coxsackie virus. In 1948 he was elected F.R.C.P., and last year he presided over the Royal Microscopical Society, the honorary editor of whose journal he had been for many years. He was also chairman of the abstracting services consultative committee of the Royal Society.

Of these busy and varied years S. S. B. G. writes:

"A genial and versatile personality, Findlay had a great capacity for making friends with all sorts and races of men, and it was not uncommon to find an African, an Indian, a Pole, or a Frenchman waiting in his anteroom to renew an old and valued acquaintance. Nor were these international friendships confined to periodic exchanges of small talk. There is good reason to suspect that his advice and aid were often sought, and generously given. He wore a perpetual air of boyish good humour; indeed I have only once seen him genuinely angry—when a newspaper had rather shamefully betrayed a confidence. He was the most approachable of men, and had that complete absence of class-consciousness which is so refreshing to encounter in this age of the battle of the income-groups.

"The range of his interests was impressive. The editor's room was always littered with great numbers of books and periodicals on every conceivable subject from viruses to witchcraft. How he found time to read them all remains a mystery, but he undoubtedly did read them. Aided by a prodigious memory, he was always willing to transfer at a moment's notice some of this store of knowledge to paper. He wrote rapidly and well on all sorts of matters. It is unfortunate that our hope that he would continue to entertain and inform us for many years is not to be fulfilled."

At his home at Radlett, Marshall Findlay shared with his wife and two daughters a happy family circle. A devoted husband and father, he was content with a simple life which his companionship and happy personality enriched for others. He died on March 14.

ROBERT WILLIAM DODGSON

O.B.E., M.D. Lond., M.R.C.P.

Dr. R. W. Dodgson, who was a relative of "Lewis Carroll," died on March 4 at his home in Conway. He will be remembered for his work on typhoid fever and particularly its transmission by mussels.

He was born at Wigton, in Cumberland, in 1871, and educated at Owens College, Manchester, and St. Mary's Hospital, Paddington, where he qualified in 1895. The following year he took the M.B. Lond., and in 1898 he obtained a gold medal in the M.D. examination. He was appointed assistant pathologist at St. Mary's Hospital, and in 1899 he went to South Africa as a special service medical officer to investigate results of anti-typhoid inoculation amongst British troops. From 1901 to 1903 he acted as director of the Government research laboratory at Cape Town. In 1912 he was a member of Sir Almroth Wright's team which went to Johannesburg to inquire into the high death-rate from pneumonia among native workers in the gold mines. This investigation led to the introduction of prophylactic inoculation.

In 1914, after a round of visits to Continental laboratories to compare their methods with our own, he reached England from Germany just four days before war was declared.

The following year he was appointed bacteriologist at the Ministry of Agriculture and Fisheries research station at Conway. In 1921 he was promoted to principal naturalist and he later became director of the station, a post which he held till 1937, when he was appointed consultant for shellfish services before retiring two years later. It was at Conway that he carried out his research into the transmission of typhoid fever by shellfish. He installed large tanks in which the mussels were laid in chlorinated sea-water and then washed in fresh water, so that free from all pollution they were sent in sealed bags to the fishmongers. He described this work in his pamphlet *Shellfish and the Public Health* and in his monograph on *Mussel Purification* which appeared in 1928. His service was recognised by his appointment as O.B.E.

KONRAD DOBRINER

M.D., D.Med.Sci. Munich

MANY engaged in the biochemistry of cancer and in related fields will have heard with regret of the death in New York on March 10 of Dr. Konrad Dobriner of the Sloan-Kettering Institute and Memorial Hospital Center.

Born at Elberfeld in 1902, he graduated from the University of Freiburg in 1925, and shortly afterwards received the degrees of doctor of medicine and doctor of medical science of the University of Munich. After emigrating to the United States in 1933, he worked as a research fellow in the University of Rochester Medical School from 1934 to 1936, and later for three years at the hospital of the Rockefeller Institute. In 1939 he was appointed head of the department of research chemistry of the Memorial Hospital, and he became a member of the Sloan-Kettering Institute in 1947, with the additional title three years later of associate professor of medicine in Cornell University Medical School.

Dr. Dobriner was the author of some 80 contributions to the medical and scientific literature, either alone or jointly with such workers as C. P. Rhoads, L. F. Fieser, S. Lieberman, R. N. Jones, T. F. Gallagher, and C. C. Stock. His earlier interests lay in the field of porphyrin excretion, and later topics included the metabolism of specific carcinogens such as 1 : 2 : 5 : 6-dibenzanthracene, β-naphthylamine and dimethylaminoazobenzene, and the carcinogenicity of benzidine.

"Of recent years," writes A. H., "Dobriner had contributed largely to the establishment of the patterns of urinary excretion of the steroid hormones in normal and pathological states, the application of infra-red spectroscopy to steroid structure and metabolism, and the study of the effects of cortisone and related steroids on the growth of experimental tumours. From these later researches he was gradually evolving a view and interpretation of the rôle of adrenal cortical dysfunction in the inception and development of malignant disease as a whole. A welcome visitor to England, he had taken part in various symposia at the Ciba Foundation and at other meetings elsewhere, and his friends had looked forward to meeting him at the International Congress of Biochemistry in Paris this summer. Many not only in the country of his adoption but far beyond it will mourn Dobie as a valued colleague and generous friend."

Diary of the Week

MARCH 30 TO APRIL 5

Tuesday, 1st

Royal College of Physicians, Pall Mall East, S.W.1
5 P.M. Prof. Robert Platt: Structural and Functional Adaptation in Renal Failure. (First of two Lumleian lectures.)
Royal Eye Hospital, St. George's Circus, S.E.1
5 P.M. Mr. T. M. Tyrrell: Cataract Extraction.

Wednesday, 2nd

Royal College of Surgeons, Lincoln's Inn Fields, W.C.2
5 P.M. Mr. S. M. Cohen: Peripheral Aneurysm and Arteriovenous Fistula. (Hunterian lecture.)
Royal Society of Medicine, 1, Wimpole Street, W.1
8 P.M. *Section of Surgery.* Dr. Hayes Martin (New York), Dr. A. Tailhefer (Paris), Sir Stanford Cade: Treatment of Cervical Metastatic Cancer.
Royal Eye Hospital
5.30 P.M. Mr. Howard Reed: Visual Fields.
Royal Institute of Public Health and Hygiene, 28, Portland Place, W.1
3.30 P.M. Prof. R. S. Illingworth: Disturbances of Sleep in Children.
Manchester Medical Society
4.30 P.M. (University of Manchester.) *Section of Medicine.* Dr. Lawrence Kilroe: All in the Day's Work.
Yorkshire Society of Anæsthetists
8 P.M. (Leeds General Infirmary.) Dr. G. Steel: Theoretical and Practical Aspects of Therapeutic Nerve Blocking.

Thursday, 3rd

Royal College of Physicians
5 P.M. Professor Platt: Structural and Functional Adaptation in Renal Failure. (Second of two Lumleian lectures.)
Royal College of Surgeons
5.30 P.M. Sir Charles Symonds: Intracranial Thrombophlebitis.
University of Oxford
5 P.M. (Radcliffe Infirmary.) Dr. T. N. MacGregor: Significance and Mechanism of Menstruation. (Litchfield lecture.)
Royal Society of Medicine
8 P.M. *Section of Neurology.* Dr. J. St. C. Elkington, Prof. R. H. S. Thompson, Dr. W. B. Matthews: The Peripheral Neuropathies.
Royal Army Medical College, Millbank, S.W.1
5 P.M. Prof. M. L. Rosenheim: Treatment of Hypertension.
Royal Eye Hospital
5.30 P.M. Miss M. Savory: Detachment of the Retina.
Association of Clinical Pathologists
4.30 P.M. (City Council Chambers, Portsmouth.) Opening scientific session of three-day meeting.
Midland Medical Society
8.15 P.M. (Birmingham Medical Institute, 154, Great Charles Street, Birmingham, 3.) Mr. W. H. Bond: Oral Cancer.

Friday, 4th

Royal College of Surgeons
5 P.M. Sir James Learmonth: After Fifty-six Years. (Lister Oration.)
Royal Society of Medicine
5.30 P.M. *Section of Anæsthetics.* Prof. R. J. S. McDowall: Asphyxia and the Electrolyte Balance.
Institute of Diseases of the Chest and Institute of Cardiology
5.30 P.M. (London School of Hygiene, Keppel Street, W.C.1.) Mr. Norman Barrett: Injuries to the Heart.
Eugenics Society
5 P.M. (26, Portland Place, W.1.) Dr. J. A. Fraser Roberts: Genetics of Mental Deficiency. (Galton lecture.)
Society of Anæsthetists of South Wales
7.30 P.M. (Cardiff Royal Infirmary.) Anæsthetic films.
Whipps Cross Hospital Medical Society, Whipps Cross Hospital, E.11
8.30 P.M. Dr. Joan Taylor: Diarrhœas of Bacterial Origin.

EMERGENCY BED SERVICE.—In the week ended last Monday applications for general acute cases numbered 1100. The proportion admitted was 89·75%.

Notes and News

NATIONAL FORMULARY, 1952

A NEW edition of the formulary is published this week. The notes for prescribers have been expanded by the addition of further monographs, and a pharmacological classification will now help the prescriber to recall those preparations which have similar actions or contain a particular drug. The list of approved non-proprietary names and their equivalents will be particularly useful in saving time and confusion. The general section of the formulary has been rearranged with English headings to the subsections, but the Latin names are retained for the individual formulæ. Prescriptions with no pharmacological justification have been dropped, but this principle has been waived in favour of some traditional and popular medicines. Doctors may miss some old friends, but they are, of course, in no way restricted to preparations in the formulary. The changes make it better than ever. The publishers are the British Medical Association and the Pharmaceutical Press, 17, Bloomsbury Square, London, W.C.1, and the price is 4s. 9*d.* post free or 7*s* 11*d.* post free for an interleaved copy.

B.M.A. IN THE MIDDLE EAST

DOCTORS from as far afield as Bahrein and the Lebanon assembled in Bagdad for the annual meeting of the Middle East Branch of the British Medical Association on March 4 and 5. Sir John Troutbeck, the British Ambassador, recalled that Bagdad was once the centre of the medical world: and "those who are Scotsmen among you may think that it might still be so today if its place had not been usurped by Edinburgh." The medical profession in Iraq had been built up in the closest association with the British, and the growing international importance of the Iraqi medical profession and of the Royal Medical College in Bagdad was clearly evident. The Ambassador was followed by Sayyid Majed Mustapha, the minister for social affairs, and Prof. Hashim al-Witry, dean of the medical faculty.

The scientific proceedings were opened by Prof. F. A. R. Stammers (Birmingham), who spoke on Fluid, Crystalloid, and Protein Balance in Surgery. Dr. F. Akrawi, professor of venereology at Bagdad, discussed bejel, which is a treponemal disease resembling syphilis, endemic in some parts of the Middle East. Clinically, bejel resembles syphilis except for the absence of the primary sore, the rarity or absence of neurovisceral complications, and doubt about its hereditary transmission. Professor Akrawi regards bejel as syphilis modified by the conditions under which it exists.

A lecture on W.H.O. in the Middle East, by Dr. W. H. Crighton, public-health administrator for the Eastern Mediterranean Regional Office of W.H.O., was followed by a discussion in which Dr. W. H. Ford Robertson (Beirut) suggested that insufficient attention had been given to mental health in the Middle East, and Prof. A. M. Critchley (Bagdad), hon. secretary of the Middle East Branch of the B.M.A., declared that the W.H.O. services for acquiring and imparting information could be improved.

THE MEDICAL DIRECTORY

THE two volumes of *The Medical Directory 1952*[1] follow the pattern of last year, but the number of medical practitioners listed has increased by 2174 (making a total of 81,846); the number of pages by 56, and the price by 9*s*.

University of Cambridge

The honorary degree of SC.D. is to be conferred on Sir Gordon Gordon-Taylor.

Dr. V. B. Wigglesworth, F.R.S., has been appointed Quick professor of biology.

Dr. Wigglesworth, who is 52 years of age, was educated at Repton. In 1917 to 1918 he served in France with a commission in the Royal Field Artillery. On demobilisation he entered Caius College, Cambridge, of which he was a scholar. In 1922 he held a Frank Smart studentship at Caius College, and in 1926 he graduated B.CHIR. from St. Thomas's Hospital. The same year he was appointed lecturer in medical entomology at the London School of Hygiene, and in 1936 he became reader in entomology in the University of London at the school. In 1939 he was elected F.R.S., and in 1944 he joined the Agricultural Research Council's unit of insect physiology at Cambridge as director. He also holds a readership in entomology in the university and a fellowship at Caius College. His published work includes, besides many papers on comparative physiology, two monographs on insect physiology.

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[1] London: J. & A. Churchill. 1952. Pp. 2824. £3 12*s*.

University of Manchester

On May 21 the honorary degree of D.SC. is to be conferred on Prof. Alexander von Muralt who holds the chair of physiology in the University of Berne.

University of Dublin

At a recent examination, the following were awarded the diploma in gynæcology and obstetrics:

Mary Abraham, Abanindranath Basu, J. P. Botha, Gopal Vasudeo Chaphekar, Thin Mann Chin, E. F. Harben, Andy Joubert, Satyendu Kumar Kundu, Durgacharan Mukhopadhyay, Dulcie G. Rayment, Harbans Lal Suri.

Royal Sanitary Institute

The International Health Congress, organised by the institute, is to take place this year at Margate from April 22 to 25 under the presidency of Lord Moran, who will give the opening address. Dr. Brock Chisholm, the director-general of the World Health Organisation, will also speak.

Proposed Charge on Prescriptions

On March 20 Mr. Harry Crookshank, the Minister of Health, received a deputation representing the General Medical Services Committee and the Central National Health Service (Chemist Contractors) Committee. This deputation explained the difficulties that doctors and chemists, more particularly in rural areas, would have in collecting the proposed 1*s*. charge on prescriptions. Further discussions are to take place.

Defence of Children

An International Conference for the Defence of Children is to be held in Vienna from April 12 to 16. Thirty-eight countries are participating, and the subjects will include economic needs, education, health, and moral and cultural problems. In Britain a committee of sponsors has been set up to arrange *for the presentation of reports on the care of children in this* country. The secretary is Mrs. Emmerson, 109, Brondesbury Road, London, N.W.6.

Coal Board's Advisory Panels

The National Coal Board have set up four panels to advise them on research into medical and human problems in the coal industry. The membership of the panels is:

Epidemiology Panel.—Dr. D. D. Reid (chairman), Mr. G. Bridgemore Brown, Mr. R. F. George, Mr. J. C. Hobbs, Mr. J. F. Houldsworth, Dr. W. P. D. Logan, Dr. J. Rogan, Dr. T. D. Spencer.

Psychology Panel.—Prof. G. C. Drew (chairman), Mr. C. B. Frisby, Dr. C. G. Gooding, Mr. N. H. Mackworth, PH.D., Dr. J. Rogan, Mr. J. W. Whitfield, Dr. A. [illegible]

Physiology Panel.—Prof. [illegible]), Dr. K. W. Donald, Dr. T. [illegible] R. Passmore, Dr. J. Rogan, Dr. [illegible]

Industrial Medicine Pane[illegible]), Dr. A. J. Amor, Prof. R. C. B[illegible] E. Howell, Dr. T. H. Jenkins, [illegible]

Dr. J. S. McLintock, assistant to the board's chief medical officer, is the secretary of the panels.

Medical Education in India

New Zealand's contribution of £250,000 to India under the Colombo Plan is to be used for building and equipping the All-India Medical Institute in Delhi. The New Zealand government have promised to provide a total of £1,000,000 for the scheme in the coming three years. The foundation stone of the institute will be laid in April, when Mr. J. T. Watts, New Zealand's minister for industries and commerce, visits India. The institute will provide facilities for training health personnel, fostering research in all branches of medicine, and offering postgraduate training. The government of India are also developing, in collaboration with UNICEF, the existing maternity and child-welfare section of the All-India Institute of Hygiene and Public Health, Calcutta, into a department of maternal and child health to serve as a national training-centre for child-health workers, with certain international obligations.

Speaking at the Glancy Medical College, Amritsar, Rajkumari Amrit Kaur, the health minister, said: "I am quite sure that all governments will have to provide adequate emoluments to whole-time teachers of all categories in our medical colleges so that the ablest in the profession may be drawn to the fields of research and teaching." The Rajkumari added: "Personally, I have no doubt that we should move as rapidly as circumstances permit towards the goal of no private practice for doctors in government service, and adequate remuneration for them. *Pari passu* with this, we should levy a per caput minimum contribution towards health insurance so that everyone may be entitled to get free treatment and at the same time be proud to feel that he is a contributor in a great humanitarian endeavour."

West End Hospital for Nervous Diseases

From April 17 to May 29 on Thursdays at 5.30 P.M. a cours of lectures and demonstrations on treatment in psychiatr will be given at the department of psychiatry of the hospital 48, Cosway Street, off Marylebone Road, London, W.1.

Arrangements for Inpatients

Arrangements for the reception and welfare of hospita inpatients in England and Wales are being examined by committee, appointed by the Central Health Services Council which includes Sir Ernest Rock Carling and Sir Willia Gilliatt. The committee are basing their review on the repor made to the Scottish Health Services Council last year.

Wessex Rahere Club

The spring dinner will take place at the Royal Clarenc Hotel, Exeter, on Saturday, April 19, when Mr. C. Naunto Morgan will be the guest of honour. Membership of the clu is open to all Barts men practising in the West Country Further details may be had from Mr. A. Daunt Batema the hon. secretary, 3, The Circus, Bath.

Le Collège International des Chirurgiens

The following meetings of the college have been arranged:

French Chapter, University of Bordeaux, May 13 and 14.
Spanish Chapter (Catalonian section), University of Barcelon May 16, 17, and 18.
International Assembly at the University of Madrid, May 20-23
Austrian Chapter, Vienna, May 26 and 27.
Dutch Chapter, Amsterdam, May 29 and 30.

Further information may be had from the secretary of th British chapter, Dr. J. F. Brailsford, 20, Highfield Road Edgbaston, Birmingham, 15.

Appointments

HAGGER, A. O., M.R.C.S.: asst. M.O., Eastern Region, Britis Railways.

MACLEAN, C. D. T., M.B. Glasg., M.R.C.P., D.M.R.D.: part-time consultant diagnostic radiologist, Charing Cross Hospital, London.

PEARCE, A. J., M.B. Birm.: appointed factory doctor, Birmingham West district, Warwick.

SHAW, J. D. F., M.R.C.S.: asst. school M.O., City of Nottingham education committee.

SIMPSON, N. R. W., M.B. Lond., D.P.M.: consultant in physical medicine to the Leicester hospitals.

WATSON, R. T. B., M.B. Glasg., D.P.H.: asst. tuberculosis physician, Lanarkshire.

Appointed Factory Doctors:

GLENN, R. W., M.B. Lond.: Haywards Heath district, Sussex.
GREIG, AGNES, M.B. Edin.: Kirkcaldy district, Fife.
WHITWORTH, HENRY, M.B. Lond.: St. Agnes district, Cornwall.

The Terms and Conditions of Service of Hospital Medical and Dental Staff apply to all N.H.S. hospital posts we advertise, unless otherwise stated. Canvassing disqualifies, but candidates may normally visit the hospital by appointment.

Births, Marriages, and Deaths

BIRTHS

CRITCHLEY.—On March 19, at Harrogate, the wife of Dr. J. M. A. Critchley—a son.

DONALD.—On March 19, in London, the wife of Dr. Ian Donald [illegible]

[illegible] 20, in London, the wife of Dr. J. D. [illegible]or.

HARROLD.—On March 17, in London, the wife of Dr. A. J. Harrold—a daughter.

MOREL.—On March 22, at Barnstaple, the wife of Mr. Mervyn Morel, F.R.C.S.—a daughter.

MUIR.—On Feb. 25, in London, the wife of Mr. Ian Muir, M.B.E., F.R.C.S.—a son.

WILKINSON.—On March 18, in London, the wife of Dr. R. S. Wilkinson—a daughter.

MARRIAGES

GRUBB—BROWN.—On March 21, in London, Dermot O'C. Grubb, to P. Jane Brown, M.B. (formerly Rickword).

JENKINS—EVANS.—On March 18, at Gilfach Goch, Glam, Ritchie T. Jenkins, M.R.C.P., to Eileen Joyce Evans.

DEATHS

CROSFIELD.—On March 20, at Broadstairs, Arthur Mellor Crosfield, L.R.C.P.E., formerly of Leicester, aged 79.

ELLIS.—On March 18, Edward Alfred Ellis, B.A., M.B. Dubl., of Great Yarmouth, aged 49.

ELLISON.—On March 19, Philip Oswald Ellison, M.B. Lond., of Gerrards Cross.

MCELLIGOTT.—On March 19, Maurice Gerald McElligott, F.R.C.S.I., of Listowel, co. Kerry, formerly of Bushey Heath, aged 83.

MUIRHEAD.—On March 4, in Sheffield, William Martin Muirhead, M.B. Sheff., D.O.M.S.

the theatre in order to check the findings; but if the radio- gist was misled by the marker, it is unlikely that the surgeon ould detect the error unless he had elicited contrary clinical idence.

The positioning of the patient and other factors of chnique should, where possible, give standard and niform radiographs comparable with films taken at her times; but standard positions are not always ossible in seriously ill patients or with surgical fixation. adiographs taken in unusual positions may be mis- terpreted because the cause for the position is not ppreciated. Though we are cautioned to "make no aste in time of trouble," the demand for wet films has ecome a habit. There are relatively few radiographs hich cannot, with advantage to the patient, await the adiologist's report; failure to do so takes the responsi- ility from the radiologist, who may have asked for rther radiographs to give more useful evidence to the linician. Why should not the radiologist be sent for hen he is needed?

In 1933 I showed that in certain conditions, notably in erthes's disease and other lesions associated with avascular ecrosis of bone, that radiography could be successfully sed to show when normal function could be permitted. This as a definite advance. Previously, surgeons had unsuccess- ully relied on clinical judgment, and the teaching was that o matter what you did with the limb in Perthes's disease, you failed to immobilise it, or immobilise it for six or even ight months, the same sequence of changes with deformity nd early osteo-arthritis followed.

I showed that in Perthes's disease the bone of the epiphysis nd its neighbourhood remained plastic for upwards of four years; as long as the radiographs showed incomplete estitution the plasticity continued, and deformity resulted f weight bearing was permitted, even with no clinical signs of active disease. Whereas, if weight-bearing was stopped when the disease showed its earliest radiographic signs, and forbidden until the radiographs showed complete restitution of the epiphyses, the sequence of changes was not actually prevented, for the dead bone has to be reconstituted, but deformity was avoided and the healed joint showed little abnormality. This advice has been proved to be correct. Now that we know the time-table of the disease there is no need for radiographic examination more often than every six to twelve months.

The practice of radiographic control for many conditions has become established, but not always on the same reasoning or foundation. In Perthes's disease and other lesions associated with avascular necrosis I advised that radiographic control should check, rather than incite, surgical and other activities. Now the reverse tendency is apparent, particularly in the treatment of fractures; the radiographic features are the cause of increased surgical interference. The lesion is repeatedly radiographed, even though restitution to normal is almost impossible in many cases. After each manipulation there is still some deformity which is thought capable of correction, and repeated manipulations are performed. In such cases active surgical measures are dictated to the surgeon by the radiographic appearances, and sometimes treatment would be more successful without this dictation. Excellent clinical and radiographic results are seen in cases where the surgeon has depended on his own experience and skill rather than radiographic control.

An orthopædic surgeon was called out one night to treat a comminuted fracture of the lower end of the humerus. He reduced the deformity and put the limb in plaster, instructing the patient to see me next day. Radiographs were taken through the plaster, and during my absence the surgeon called at my rooms, saw the radiographs, and instructed, indeed, compelled, my radiographer to destroy them in his presence. He later complained of the "rotten" radiographs, and said that though the fragments appeared to be in a dreadful position he knew that the position was good and he wanted me to show it for he would not have the practitioner see otherwise. By rotating the patient under the screen further radiographs were taken which were more to the surgeon's liking. This did not seem reasonable to me at the time, but when the patient consulted me a year later for indigestion, he spoke of his great admiration for the surgeon; and when I asked him how the elbow was, he repeatedly flexed and extended both forearms, saying "I don't know which it was." A lesser surgeon might well have interfered with his primary reduction and consequently got a bad result.

The value of specialised techniques has been much overrated. In my early years the use of non-medically qualified assistants was often discussed. In those days before precision radiography, the quality of the radiograph depended on individual skill and ability. Many pictures were really indecipherable, but they were boldly interpreted as if self-evident. I was able to show that the assistant ("porter" or "orderly" he was usually called) kept his job by producing good radiographs which somebody might be able to interpret, whereas those taken by some radiographers (as medical men were then called) were so poor that neither they nor anyone else were justified in interpreting them. Today we see many tomographs whose quality permits far too much latitude in interpretation and does not justify the great significance attached to them. Many such investigations could reasonably be dispensed with.

Some contrast media are toxic and should be used only when fresh and from a reliable source. Media should be kept in a place where no dangerous drugs are permitted, lest they are confused or contaminated. They should all be used at body-temperature, particularly when injected; even iodised oil injected into the trachea has induced fatal inspiratory spasm. What seems to be the simplest method can be disastrous or even fatal, particularly in the presence of an obstructive lesion.

Every radiologist has seen the results of faulty injections—e.g., iodised oil in the paratracheal and paravertebral tissues, perivascular injections, and extravasation of injected fluids into the kidney. None of these injections should be made without good reason and until every other method likely to yield essential evidence has been tried; and because they carry a risk which it is sometimes justifiable to take, they should not be given except by someone with the necessary skill; otherwise the investigation will be useless and the risks, therefore, unwarranted. A wide knowledge of the normal appearances is needed for correct interpretation, since the variations of normal are infinite. If our knowledge was sufficiently comprehensive we should see that these variations passed imperceptibly into one another, but most of us have very little knowledge of radiological visualisation and the extreme limits of normal are very likely to be mistaken for evidence of disease. The reaction of patients to injected fluids may be far more severe than expected and this in itself may mean radiographs of little value. In general the less discomfort given to the patient the more valuable will be the results.

INTERPRETATION OF THE RESULTS

It is most important that we should use all the evidence which the examination offers, but we must not read into it what is not there. The statements made in court when radiography is admitted in evidence show how blind is he who won't see and how creative are the eyes of those who wish to see. Evidence of this kind which the intelligent but inexperienced layman cannot decipher, should be interpreted for him by an unbiased authority.

The radiographs heed no specialty. He who takes the responsibility of interpreting them must have knowledge not only of his specialty but also of the radiology of all structures in the area, widely separated though they may be anatomically. A predominant interest in any one system may blind the observer to other evidence obvious to those who seek it. Even radiologists who are aware of the possibility, suffer in this way, and they come to recognise, with experience, shadows and appearances that they did not previously see.

Some radiographic appearances are characteristic and unequivocal—e.g., metallic foreign bodies, and some gall-stones, renal stones, and lesions of bone, stomach, and intestine. The radiologist's report should record these findings in language readily understood by the patient's doctor. Unfortunately there is a trend in radiology, as in all specialties, to talk a jargon which only the specialists can understand (or do they?). To illustrate this failing I said in my Rotunda contribution (Brailsford 1947):

> Little has been gained from the substitution of the simple terms round, oval, flat, wedge-shaped, or oblique by the quasi-scientific expressions mesatipellic, doliochopellic, brachypellic, platypellic, &c., other than the doubtful value of the elevation of the terms above the appreciation of the general practitioner.

One group of writers state: "For simplicity we have described five borderline or mixed types, the anthropoid-gynecoid, the gynecoid-flat, the android-anthropoid, the android-flat, and the android-gynecoid." But they said in the same paragraph: "The term 'flat' is preferable to the term 'platypelloid.'"

I was taught this lesson of clear and simple language by a wise physician and friend who, within a few weeks of my appointment as assistant radiologist, called me to the ward where he was teaching.

> He gave me a radiograph and asked me to tell him what were the shadows visible to the right of the upper lumbar spine: to which I answered "gall-stones." He then showed me my report in which I had described a collection of shadows in the region of the gall-bladder. This, he said, was shirking my responsibility. I must take my share of responsibility, as he had, and whenever I could state definitely *it was my duty to do so, and not leave it to the clinician,* who saw very much less radiology, to do my job for me. A technician could do what I had done, but I was a doctor and he expected me to bear responsibility for what I did. If I did so, he said, I would be more careful in my reports, and as my experience grew I would be able to give him the benefit of it in more and more cases. "It may be that your opinion is in opposition to that of your clinical colleagues, but if it is based on knowledge and sound judgment, you have a duty to the patient to state it; sound clinicians will seek your opinion rather than your acquiescence." He then drew *attention to my signature. This he said should be clear, not* an undecipherable initial, and so be free from the suspicion that I was shirking responsibility for the reports.

I have found this advice of great value throughout my career, but its results have not always been welcomed. To be in error in company is often acknowledged as good fellowship, and it is certainly much less unpleasant than to be lonely in the right.

Though increasing experience leads to more accurate identification, we also come to know that many different lesions of widely varying significance can give similar radiographic appearances. The dogmatic utterances of enthusiasm give place to the balanced but perhaps less confident statements of experience. Far too much radiological interpretation is shallow, and based on what I call "atlas" or "picture" radiology—the spot diagnosis. The radiograph is compared with the picture book, and the title beneath the picture which, in the observer's opinion, most closely resembles it is now given to the lesion. I have been amazed at the recognition of similarity in many cases which I would have thought bore no resemblance.

> This "atlas" teaching is not confined to radiology, and it is seen perhaps just as extensively in histopathology. The teacher selects what he regards as typical specimens of a condition and the student is taught to recognise these specimens. He is not taught that classical specimens are rare and that variations in pathology, as in normality, are infinite; consequently the recognition of certain common features in widely different lesions dictates his opinion.

There are many conditions which at one stage or another will simulate other diseases by their X-ray appearances. In such a case it would be unwise venture a diagnosis on one film alone. The histo and clinical findings may often help in making a defin diagnosis. I once heard a clinician say that biopsy w necessary to distinguish a congenital short œsopha from carcinoma, because the radiographic signs alo were insufficient. But surely only if there is no su thing as clinical medicine?

A radiologist's report which sets out a number conditions of somewhat similar appearance, leaving t clinician to take his choice, is relatively valueless a even confusing.

> Recently I saw some films of a chest which showed discr opacities on one side. The report stated: "? new grow ? tubercle, ? pneumoconiosis, ? secondaries, ? fibrosis fr gas, ? unresolved pneumonia." The radiograph showed fractures of the ribs on the affected side and thickening of t pleura. *The definition and distribution of the opacities a the other radiographic evidence made the diagnosis of ossific tion in the pleura following hæmothorax the probability.*

Time is often necessary to establish beyond dou the essential cause of the radiographic appearances a particular patient. In some cases only necrop reveals the truth, and in the meantime the signs a symptoms may be so vague and widespread that it impossible to locate the cause by any means. A sp diagnosis on a single film may mislead, and much great accuracy comes from serial radiography and a study the sequence of changes. By this means it is possib to distinguish readily between such widely differe conditions as tuberculous coxitis and Perthes's diseas Time is particularly important in distinguishing betwe inflammatory and neoplastic lesions. It is often sa that we must not wait for a diagnosis, and to avoid del more and more biopsies are performed. But biops *often fails or gives the wrong answer, even in lesions* whic can be more accurately diagnosed by radiology. Biops is considered by many to be reasonable for lesions in th limbs or superficial tissues which can be excised; bu it has little to recommend it for lesions of the trunk whic cannot be removed.

THE USE OF THE RADIOLOGIST'S REPORT

I believe it is the duty of the radiologist to recognis his responsibility when he examines the patient an writes his report. Edwards (1950) remarked:

> "There is a tendency amongst the less experienced radio logists to include advice to the clinician in their reports It is far better for the latter to be factual, and not advisory To quote an example: 'Filling defect lesser curve ? simple ? malignant. Advise repeat X ray in two months.' Such a report should end at 'malignant.' Better still would it be if it read: 'There is a filling defect on the lesser curve which may be caused by malignant disease.'"

I agree that on superficial observation this report appears useless, but I cannot approve Mr. Edwards's advice. The only value of the report may lie in its first sentence, since the defect may have passed unnoticed by anyone less experienced in the normal and its variations. But it could be that this abbreviated report was fundamentally sound and based on a careful investigation by an experienced radiologist. The criticism suggests that the radiologist is only a technician, whose duty it is to give suggestions which will provide an excuse for surgical exploration. It is surely the duty of the radiologist, as a doctor, to give such advice as he is specially competent to give on the diagnosis and treatment of the patient. The physician or surgeon should encourage and consider such advice. Let the clinician take the responsibility of ignoring it if he will; a recital of the cases in which disaster has followed would show that it is a very grave responsibility when the clinician is not the better judge of the available evidence. "Profess not the knowledge therefore that thou hast not" remains good advice for radiologist and clinician.

During a visit to the United States I attended a number of hospital conferences where all the available evidence about a patient was pooled and discussed. Each specialist presented his own evidence, as he alone could, and the final decisions showed a more balanced judgment. My previous suggestion (Brailsford 1945) that such conferences should be the basis of ward classes in this country was rejected in spite of strong supporting evidence.

It is not only the puzzling cases which should be so discussed—their elucidation may be impossible even with the fullest discussion. The apparently simple diagnosis may have been based on insufficient consideration; the spectacular evidence of radiology is particularly prone to misinterpretation. Ruskin puts the point clearly: "Knowledge is infinite and . . . the man most learned in human estimation is just as far from knowing anything as he ought to know it as the unlettered peasant."

REFERENCES

Brailsford, J. F. (1940) Medical Annual. London; p. 507.
— (1945) *Brit. J. Radiol.* 18, 249.
— (1946a) *Practitioner*, 157, 200.
— (1946b) *Brit. J. Radiol.* 19, 453.
— (1947) *In* Rotunda Hospital Centenary Transactions. Dublin; p. 338.
Edwards, H. C. (1950) *Brit. med. J.* i, 973.
Santos, Carlos (1944) A Radiologia perante o Problema dos Corpos Estranhos. Lisbon.
Walshe, F. M R. (1950) *Brit. med. J.* ii, 379.
Walton, Sir James (1950) *Ibid*, i, 206.

SELF-DEMAND FEEDING IN A MATERNITY UNIT

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With statistical help from

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B.A. Camb.

From the Department of Mathematics, University of Sheffield

IT has been suggested that most of the common difficulties in infant feeding are man-made (Illingworth 1949). While considering possible reasons for the higher incidence of successful lactation in primitive communities than in more civilised ones, it occurred to one of us (R. S. I.) that one factor which might contribute to this might be an elastic feeding schedule. A rigid feeding schedule could hardly have been intended by nature. It was thought that a man-made rigid feeding schedule might perhaps have a harmful effect on the establishment of lactation.

The reasoning which led to the supposition was as follows. Waller (1946, 1950a and b) considered that insufficient emptying of the breast was probably the commonest cause of the failure of lactation. Olmsted and Jackson (1950) recorded the total number of feeds taken by 100 breast-fed babies on a self-demand schedule in the first week of life. The average numbers were as follows:

Day	1	2	3	4	5	6	7
Number of feeds	6·2	6·9	8·1	8·6	8·5	8·3	7·9

Experience at the Jessop Hospital for Women, Sheffield, where self-demand feeding has been practised for the last two years, showed that it was common for babies to demand very frequent feeds from the fifth to the eighth day of life. There seemed to be a peak in the frequency of feeds at this time. A rigid feeding schedule would, so to speak, carve off the summit of this peak in many babies by keeping them to a fixed number of feeds (5–7) in the twenty-four hours.

It was thought possible that babies fed on a self-demand schedule might take more milk from their mothers because of the more frequent feeds. A baby fed on a self-demand schedule, furthermore, might suck better at the breast than a baby on a rigid schedule, for a baby who is kept waiting and crying for a long time for a feed is apt to become tired and to swallow air as a result of crying, and so to suck badly when taken to the breast.

We did not know whether the over-all quantity of milk taken by frequent feeders would be greater than that taken by infrequent ones. It was realised that in some cases frequent demands for food could be simply explained by an unsatisfied appetite due to an inadequate supply of milk. If it were found that babies fed on a self-demand schedule usually took more milk from their mothers, this would be important, for it would be exactly what was needed to secure proper emptying of the mother's breast and so the avoidance of overdistension, the danger of which has been so strongly emphasised by Waller.

We were unable to find any experimental work on the relation of the feeding schedule to the establishment of lactation, though there were a very large number of statements about the importance of a rigid feeding schedule, or about the superiority of three-hourly or four-hourly feeds, without any apparent evidence to support those statements. We therefore made the experiment described below. The plans for the experiment were laid with the help and advice of the matron (Miss M. J. W. Taylor) and the sisters in the maternity wards, to whom we are greatly indebted.

EXPERIMENT

The aim of the experiment was to feed 100 babies on a self-demand schedule and 100 on a rigid schedule, and to compare the weight gain in the two groups, the incidence of overdistension of the breast in their mothers, and the incidence of full breast-feeding on discharge and at the age of 1 month. All the babies were to be included in the experiment, except prematurely born ones and those showing any form of cerebral irritability.

The babies are housed on two floors. Except for six small wards, one holding 8, two holding 3, and the remainder holding 2 women each, all the accommodation consists of single rooms. In all the cases the baby is kept in a crib at the side of the mother day and night, and not taken away from her for any purpose, such as bathing or napkin changing. All the babies were under the care of one pædiatrician (R. S. I.) and one full-time resident pædiatric registrar. One senior registrar (D. G. H. S.) helped the latter in the daily supervision of the details of the experiment. Although the babies on the two floors were under the same pædiatric supervision, and there were no known differences in the management of the babies, it was felt advisable to switch the experiment when half-way through, so that the ward which had used a rigid schedule would change to the self-demand schedule, and vice versa. The aim of this was to exclude any unknown fallacies arising from subtle differences in treatment on the two floors. Unfortunately this aim was not fully achieved, because the nurses had found that a self-demand schedule was a great deal easier for them; and, owing to a very serious shortage of nurses at the time, there was great reluctance to revert to a rigid schedule which was thought to involve more work and take more nursing-time. As a result no babies were fed on a rigid schedule on one of the two floors. Comparisons between the birth weights, weight progress, and incidence of breast-feeding for babies on a demand schedule on the two floors gave no evidence of any systematic difference between these floors.

TABLE I—NUMBERS OF BABIES IN RIGID AND DEMAND GROUPS IN DIFFERENT BIRTH-WEIGHT CLASSES

Birth-weight class (¼ oz. units)	Rigid	Demand	
		Floor 1	Floor 2
350 (5 lb. 7½ oz.)	14	13	3
400 (6 lb. 4 oz.)	30	22	10
450 (7 lb. ½ oz.)	31	26	6
500 (7 lb. 13 oz.)	24	22	8
550 (8 lb. 9½ oz.)	4	11	2
600 (9 lb. 6 oz.)	1	—	—
650 (10 lb. 2½ oz.)	1	—	—
700 (10 lb. 15 oz.)	—	—	1
Total	105	94	30

A further difficulty arose as a result of the shortage of nurses. An occasional mother was discharged home early (about the eighth day) before lactation was established, and therefore before our records were completed. Not all the totals given, therefore, are the same. The total number of babies fed by the rigid method was 106. 131 babies were fed on the self-demand schedule.

In the first two days all the babies in both groups were put to the breast six-hourly. The first feed was usually 6–12 hours after delivery, but there was no rigidity about this. If a mother wished to feed her baby immediately after birth she was allowed to do so, if the baby was in good condition. If she were exhausted by the effects of delivery, the baby would be kept away from the breast for the first twenty-four hours. Otherwise the baby was allowed two minutes on each breast at each feed on the first day, and five minutes on each breast at each feed on the second day. An ounce of boiled water was offered half-way between the *six-hourly* feeds. The reason for this rigid schedule in all the babies in the first two days was the fear that more frequent feeds might cause soreness of the nipples. It is freely admitted, however, that we have no evidence that the fear is justified. On the third day the babies were divided into two groups, for rigid or demand feeding, all babies on one floor being treated by the one, and all those on the other floor being treated by the other schedule. Babies on the rigid schedule (henceforward to be termed the "rigid group") were fed four-hourly by day and once at night (6 feeds in twenty-four hours). It will remembered that babies weighing $5^1/_2$ lb. or less birth were excluded from the experiment. Babies in t self-demand group (henceforward termed the "d group") were fed when they wanted it, day or nigh The causes of crying other than hunger in newbo babies—e.g., desire to be cuddled, and a soiled napk were explained to the mothers.

TABLE II—WEIGHT PROGRESS ON 9TH DAY OF DEMAND BABIES ON FLOORS 1 AND 2

Birth-weight group	Floor 1		Floor 2		Student's *t* for difference of means
	Mean weight progress (oz.)	No. of babies	Mean weight progress (oz.)	No. of babies	
A ..	0·87	30	0·10	10	0·39
B ..	−0·46	28	0·75	8	0·63
C ..	−2·22	31	−5·32	7	1·13

None of the values of Student's *t* is significant, nor is the mean *t* (0·72) compared with its *approximate standard error of 0·58.*

The babies were weighed naked at birth and on th *third day* and *thereafter on alternate days.* They wer classified into *groups* with *similar birth* weights f purposes of statistical analysis. Routine test feeds hav been abolished at the Jessop Hospital on the ground that they waste the nurses' time and interfere with th establishment of breast-feeding. For the purposes of th experiment, however, they were made on the sixth a eighth days, the baby being weighed before and aft every feed in the day. If the milk was expressed fro the breast as a result of overdistension or for othe reasons, the amount expressed was added to the amoun gained in the appropriate test feed.

TABLE III—INCIDENCE OF FULL BREAST-FEEDING, SORENE OF NIPPLES, AND OVERDISTENSION OF THE BREAST IN T TWO DEMAND GROUPS

—	Incidence of full breast-feeding		Incidence of soreness of nipples	Incidence o overdisten-sion of breast
	On discharge	At one month		
Floor 1	28/30 (*93·3%*)	22/29 (*75·8%*)	5/30 (*16·7%*)	5/30 (*16·7*
Floor 2	89/94 (*94·7%*)	77/93 (*82·8%*)	11/95 (*11·6%*)	16/95 (*16·9*

It is an extremely unusual practice in the hospital t give complementary feeds at any time in the first week but, if by the fifth or sixth day there was practically n milk, in spite of manual expression *after the baby* ha sucked, then small complementary feeds were given afte the breast-feeds.

Overdistension of the breast was treated on the line advocated by Waller (1946), and his definitions were used. If the baby did not relieve the overdistension, the milk was expressed manually. Stilbœstrol 10 mg. four-hourly was used in the moderate and severe cases until the overdistension was relieved.

For the purposes of the experiment "sore nipple" and "fissured or cracked nipple" (causing pain) were regarded as *synonymous.* Soreness of the nipple was treated immediately by removal of the baby from the breast, manual expression of the milk, application of *penicillin cream or gentian violet to the* nipple, and return of the baby to the breast as soon as the nipple had healed.

The babies were *followed up in the* well-baby clinic a month after birth. A baby was described as fully breast-fed at this time if, in addition to relying entirely on his mother's breasts for food, he was also gaining weight satisfactorily. Unfortunately it was impossible to follow

TABLE IV—NUMBER OF FEEDS PER 24 HOURS TAKEN BY BABIES IN THE DEMAND GROUP

No. of feeds per 24 hr.	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9
3	1 (*0·9%*)	1 (*0·8%*)	—	—	—	—	—
4	18 (*15·7%*)	9 (*7·3%*)	9 (*7·1%*)	4 (*3·1%*)	3 (*2·3%*)	4 (*3·1%*)	2 (*2·7%*)
5	37 (*32·2%*)	19 (*15·4%*)	12 (*9·5%*)	26 (*20·0%*)	22 (*17·1%*)	25 (*19·7%*)	10 (*13·3%*)
6	25 (*21·7%*)	31 (*25·2%*)	30 (*23·8%*)	45 (*34·6%*)	38 (*29·5%*)	50 (*39·4%*)	24 (*32·0%*)
7	17 (*14·8%*)	33 (*26·8%*)	39 (*31·0%*)	35 (*26·9%*)	46 (*35·7%*)	40 (*31·4%*)	20 (*26·7%*)
8	13 (*11·3%*)	20 (*16·3%*)	24 (*19·1%*)	16 (*12·3%*)	15 (*11·6%*)	8 (*6·3%*)	15 (*20·0%*)
9	4 (*3·5%*)	7 (*5·7%*)	8 (*6·4%*)	2 (*1·5%*)	2 (*1·6%*)	—	4 (*5·3%*)
10	—	2 (*1·6%*)	2 (*1·6%*)	2 (*1·5%*)	2 (*1·6%*)	—	—
11	—	—	1 (*0·8%*)	—	—	—	—
12	—	1 (*0·8%*)	1 (*0·8%*)	—	1 (*0·8%*)	—	—
Total fully recorded ..	115	123	126	130	129	127	75

TABLE V—WEIGHT PROGRESS ON 9TH DAY OF DEMAND AND RIGID BABIES

Birth-weight group	Demand		Rigid		Student's t for difference of means
	Mean weight progress (oz.)	No. of babies	Mean weight progress (oz.)	No. of babies	
A ..	0·68	40	−1·24	28	1·49
B ..	−0·19	36	−1·91	41	1·58
C ..	−2·79	38	−6·22	28	2·19*

* Significant at 5% level.

up all the babies between the time of discharge and the first visit to the well-baby clinic at the age of three weeks.

The first question to be decided is whether the "demand" babies on the two floors can safely be combined into one group. The distribution of birth weight in the three groups is shown in table I.

The mean birth weight in the rigid group was 7 lb. 4 oz.; in the demand group on floor 1 it was 7 lb. 5·4 oz.; and in the demand group on floor 2 it was 7 lb. 7·1 oz.

The babies were next divided into three groups according to birth weights:

Group A, birth weight less than 6 lb. 13¼ oz.

Group B, birth weight from 6 lb. 13¼ oz. to 7 lb. 13 oz. inclusive.

Group C, birth weight greater than 7 lb. 13 oz.

This classification produces about equal numbers of babies in groups A, B, and C. Comparisons between some corresponding results for floors 1 and 2 are given in tables II and III. These furnish no statistically significant evidence of differences between floor 1 and floor 2 in weight progress, incidence of full breast-feeding, sore nipples, or overdistension.

TABLE VI—NUMBERS AND PERCENTAGES OF CHILDREN RECOVERING BIRTH WEIGHTS BY 5TH, 7TH, AND 9TH DAYS IN DEMAND AND RIGID GROUPS

—	5th day	7th day	9th day
Demand group	15/119 (*12·6%*)	32/116 (*27·6%*)	56/114 (*49·1%*)
Rigid group	5/100 (*5·0%*)	19/98 (*19·4%*)	35/97 (*36·1%*)

There was no significant difference in the parity of the mothers, or of the duration of their stay in hospital, in the demand and rigid groups. Henceforward, therefore, the demand babies in the two floors are combined into one group.

RESULTS

Number of Feeds Taken

It has already been stated that babies in the rigid group took 6 feeds in the twenty-four hours. The number of feeds taken by the babies in the demand group is shown in table IV. The mean number of feeds in the demand group for twenty-four hours was 6·4 in those of birth-weight group A, 6·5 in group B, and 6·2 in group C. There is no significant difference between these, the over-all mean being 6·4.

It will be seen that a considerable number of babies demanded more than 7 feeds a day. On the fifth day 36 babies (28·6%), and on the seventh day 20 (15·5%), demanded 8 feeds or more. 12 babies (9·5%) on the fifth day demanded 9 feeds or more.

Weight Progress

Table V shows the weight progress of the children in the two groups on the ninth day in relation to their birth weight. The mean for the three groups is 1·75 oz., and its standard error is 0·58. It is significant on the 5% level. Thus the gain is greater for demand than rigid babies, varying from 2 oz. greater for light to 3½ oz. for heavy babies.

On the ninth day 49·1% of the demand group had recovered their birth weight, as compared with 36·1% of the rigid group (table VI). This difference is statistically significant. On the fifth and seventh days the difference is smaller, and does not attain statistical significance.

Relation between Weight Progress, Overdistension of Breast, and Soreness of Nipples

In table VII is shown the relationship between the weight progress by the ninth day and the mean of the test feeds on the sixth and eighth days. For convenience, the relationships of these variables with overdistension of the breast and soreness of the nipples were also included in this correlation analysis.* The birth-weight groups were analysed separately: but, since little difference existed between the three birth-weight groups either for the "demand" or the "rigid" groups of babies, only the over-all correlations are shown in the table.

TABLE VII—CORRELATIONS BETWEEN MEAN TEST FEED, WEIGHT PROGRESS, OVERDISTENSION, AND SORE NIPPLES

—	DEMAND (based on 103 degrees of freedom)			
	Mean test feed	Weight progress	Over-distension	Sore nipples
Mean test feed ..	—	0·562*	−0·064	−0·082
Weight progress ..	0·562*	—	0·050	−0·243*
—	RIGID (based on 104 degrees of freedom)			
Mean test feed ..	—	0·569*	0·266*	−0·288*
Weight progress ..	0·569*	—	0·206*	−0·095

* Significant at 5% level.

As one would expect, table VII shows that there is a correlation in both groups between the amount of milk taken in the test feeds and the gain in weight. The table shows that less milk is taken when there is soreness of the nipples. Overdistension of the breast tends to be associated with large test feeds.

Relation between Weight Gain and Number of Feeds Taken

A connection seems to exist between the weight gain and the mean number of daily feeds (table VIII). The gain in weight increases as the average number of daily feeds increases, an increase in the frequency of feeding causing more effect in lighter babies than in heavier ones.

TABLE VIII—WEIGHT PROGRESS ON 9TH DAY RELATED TO AVERAGE NUMBER OF FEEDS PER DAY

—	Group A	Group B	Group C
Mean increase of weight progress per additional feed during the day (oz.)	3·0	0·8	0·6
Student's t	3·29*	0·63	0·48
No. in group	39	35	38

* Significant at 5% level.

The average t for the three groups is 1·47 and is significant, having a standard deviation of about 0·58.

Table IX shows the results of a similar analysis for the test feeds on the sixth and eighth days with the number of feeds on those days. It is seen that the test feed increases as the number of feeds on the day of the test increases.

Relation of Feeding Schedule to Incidence of Overdistension of Breast and Soreness of Nipples

Table X shows that 27·4% of the mothers feeding babies on a rigid schedule developed soreness of the nipples,

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* Using dummy variable equalling 1 when the symptom was present and 0 otherwise.

TABLE IX—*TEST FEEDS ON 6TH AND 8TH DAYS AGAINST NUMBER OF FEEDS ON DAY OF TEST*

—	Group A		Group B		Group C	
	6th day	8th day	6th day	8th day	6th day	8th day
Mean increase of test feed per additional feed on the day (oz.)	3·0	1·2	2·0	1·2	1·3	1·3
Student's *t*	4·10*	1·59	1·77	1·03	1·78	1·64
No. in group	37	35	36	32	32	32

* *Significant at 5% level.*

t = 2·55 and 1·42 respectively, with the standard deviation 0·577, both of which are significant.

compared with 12·9% of those feeding babies on demand. 34·0% of the mothers feeding babies on a rigid schedule had overdistension of the breast, compared with 16·9% of those feeding babies on demand. These differences are statistically significant, having standard errors of 5·27 and 5·69 respectively.

Relation of Feeding Schedule to Incidence of Breast-feeding

Table XI shows that 64·5% of the 96 babies in the rigid group were fully breast-fed at the age of one month compared with 80·3% of 122 babies in the demand group. This difference is statistically significant (standard error = 6·1).

Relation of Overdistension and Soreness of Nipples to Incidence of Breast-feeding

It will be seen in table XII that 80·5% of the mothers in the rigid group who had overdistension were breast-feeding their babies at the end of a month, as compared with 55·9% of those who did not have overdistension. This difference is of statistical significance (standard error = 9·2).

It seems that overdistension of the breast when properly treated does not have an adverse effect on the incidence of breast-feeding, as might have been expected. The converse is the case: more women are fully breast-feeding their babies on discharge if they have had overdistension than if they have not had it. It seems likely, however, that *severe* overdistension, because of the great difficulty of expressing milk, will have an adverse effect, and certainly clinical experience suggests it.

TABLE X—OVERDISTENSION AND SORENESS OF NIPPLES IN DEMAND AND RIGID GROUPS

—	Rigid group	Demand group
Soreness of nipples	29/106 (*27·4%*)	16/124 (*12·9%*)
Overdistension of breast	36/106 (*34·0%*)	21/124 (*16·9%*)
Soreness of nipples and overdistension	6/106 (*5·7%*)	2/124 (*1·6%*)

Soreness of the nipples, however, had a bad effect on lactation (table XIII). 77·8% of the mothers who had no soreness were fully breast-feeding their babies at one month, compared with 54·8% of those who did have soreness. This difference is of statistical significa (standard error = 7·8).

DISCUSSION

It seems clear that self-demand breast-feeding favo the establishment of lactation more than does a ri schedule. Probably this is due to two factors—the bet emptying of the breast by babies fed on demand, an lower incidence of soreness of the nipples in their mothe The fact that babies fed on demand gain weight fas than those on a rigid schedule, together with the rat obvious correlation between the weight gain and t amount of milk taken from the mother, shown by t test feed, strongly suggests that the "demand" bab empty the breast better than do the babies on a ri schedule. It could, however, be argued that a mot is less likely to be worried by her baby's cries for fo if he is fed when he wants feeding, and that as a res of worrying less she produces more milk and so he ga weight better. It was shown, however, that there wa lower incidence of overdistension of the mother's bre *when their children were fed on demand*, and this shou be due to the fact that these babies empty the brea better than do those on a rigid schedule. Many of t "demand" babies had frequent feeds, and there was positive correlation between the frequency of the fee and the amount of milk taken from the mother. The is evidence, therefore, that babies fed on demand empt the breast better than do those on a rigid schedul Waller (1946, 1950a and b) has strongly emphasise the importance of the emptying of the breast for th establishment and maintenance of lactation.

TABLE XI—INCIDENCE OF BREAST-FEEDING IN DEMAND A RIGID GROUPS

—	On discharge		
	No. fully breast-fed	*No. comple-mented*	*No. artificially f*
Rigid group (101 babies) ..	89 (*88·1%*)	12 (*11·9%*)	—
Demand group (124 babies)	117 (*94·4%*)	7 (*5·7%*)	—
—	At age of 1 month		
Rigid group (96 babies) ..	62 (*64·5%*)	—	34 (*35·5*
Demand group (122 babies)	98 (*80·3%*)	—	24 (*19·7*

The lower incidence of soreness of the nipples in th demand group was unexpected. Walser (1945) said:

> "*In many cases the mounting incidence of* cracked an sore nipples is not because the nipple has little rest betwee feedings but because in many cases the baby is kept in th nursery too long after birth and brought in so infrequentl that a starving ravenous baby results and the mother's brea is damaged by the child's own efforts."

Mead (1950) referred to "primitive mothers wh nurse almost constantly and therefore never suffer fro cracked nipples because the satisfied infant does no have to draw so ravenously." It certainly seems likel that the increased hunger of the baby kept on a rigi schedule may be the cause of the higher incidence o

TABLE XII—INCIDENCE OF BREAST-FEEDING AND OVERDISTENSION IN DEMAND AND RIGID GROUPS

—	Percentage of breast-fed babies								
	All cases			Rigid group			*Demand group*		
	Over-distension	No over-distension	Difference in percentages	Over-distension	No over-distension	Difference in percentages	Over-distension	No over-distension	Difference in percentages
On discharge ..	96·5% (55/57)	89·8% (149/166)	6·7	94·4 (34/36)	84·4 (54/64)	10·0	100·0 (21/21)	93·1 (95/102)	6·9
After a month ..	82·5% (47/57)	71·3% (114/160)	11·2	80·5 (29/36)	55·9 (33/59)	24·6*	85·7 (18/21)	80·2 (81/101)	5·5

* Significant at 5% level.

TABLE XIII—INCIDENCE OF BREAST-FEEDING AND SORE NIPPLES IN DEMAND AND RIGID GROUPS

	Percentage of breast-fed babies								
	All cases			Rigid group			Demand group		
	Sore nipples	No soreness	Difference in percentages	Sore nipples	No soreness	Difference in percentages	Sore nipples	No soreness	Difference in percentages
On discharge ..	86·4% (38/44)	92·8 (167/180)	6·4	85·7% (24/28)	89·0% (65/73)	3·3	87·5% (14/16)	95·3% (102/107)	7·8
After a month ..	54·8% (23/42)	77·8 (137/176)	23·0*	48·1% (13/27)	71·0% (49/69)	22·9*	66·7% (10/15)	82·2% (88/107)	15·5

* Significant at 5% level.

soreness of the nipple. The effect on the establishment and maintenance of lactation is considerable. The effect might well be greater still if soreness of the nipples were not treated so promptly as it is at the Jessop Hospital at Sheffield.

The higher incidence of overdistension of the breast in the rigid group was interesting. Newton and Newton (1951) suggest that there is a lower incidence of overdistension in babies fed on demand than in babies on a rigid schedule. We cannot explain the unexpected finding that mothers who had overdistension of the breast were more likely than others to breast-feed their babies. It may mean that overdistension is more likely to develop when there is an abundance of milk, and that, if the overdistension is properly treated, there is good reason to think that an adequate milk-supply will be maintained. It is difficult to explain the apparent contradiction between the fact that in the rigid group there was a higher incidence of overdistension of the breast and a lower incidence of breast-feeding. It seemed that if there was overdistension in either the demand or the rigid group, the outlook for breast-feeding was good, and there was no material difference in this respect between the two groups. In the rigid group, however, if there was no distension, the outlook for breast-feeding being maintained up to the age of one month was not nearly so good as in the demand group without overdistension. Severe overdistension, however, presents considerable danger to lactation, because it is so difficult to empty the breast and involution is therefore liable to occur.

SUMMARY

106 babies in a maternity unit were fed on a rigid feeding schedule of 6 feeds in the twenty-four hours (the "rigid group"), and 131 babies were fed on demand ("demand group"). In the latter group demands were most frequent between the fourth and seventh days. On the fifth day 36 babies (28·6%) demanded 8 feeds or more, and 12 babies (9·5%) demanded 9 feeds or more.

The "demand" group gained weight faster than those on a rigid schedule. By the ninth day 49·1% of the babies in the demand group had regained their birth weight, compared with 36·1% of those in the rigid group.

There was a strong positive correlation between the weight gain and the amount of milk taken from the mother's breasts, shown by the test feeds.

There was a positive correlation between the number of feeds taken in the twenty-four hours and the quantity of milk taken from the breast in that period.

There were more than twice as many cases of overdistension of the breast and soreness of the nipple in the rigid group as there were in the demand group. 27·4% of the mothers in the rigid group developed soreness of the nipples, compared with 12·9% in the demand group. 34·0% of the rigid group developed overdistension of the breast, compared with 16·9% of the demand group.

88·1% of the babies in the rigid group and 94·4% of the demand group were discharged fully breast-fed. At the age of one month 64·5% of the rigid group and 80·3% of the demand group were fully breast-fed.

There was no significant difference between the incidence of breast-feeding in the mother who had overdistension of the breast in the rigid or demand groups either on discharge or at one month. At one month 85·7% of the mothers in the demand group were fully breast-feeding their babies, and 80·5% of those in the rigid group. This figure corresponds closely with the figure of 80·2% for the mothers in the demand group who did not have overdistension. But only 55·9% of the mothers in the rigid group who had no overdistension were breast-feeding their babies at one month.

It was concluded that self-demand breast-feeding, by causing better emptying of the breast, and leading to less frequent soreness of the nipples than a rigid schedule, had a favourable effect on the establishment and maintenance of lactation.

Our thanks are due to Dr. T. Colver for allowing us to carry out part of this investigation on his cases; Dr. M. Powell and Dr. N. Cole, the pædiatric registrars; and Miss M. J. W. Taylor, matron of the Jessop Hospital, and the nursing sisters without whose help the experiment would have been impossible.

REFERENCES

Illingworth, R. S. (1949) *Brit. med. J.* ii, 1077.
Mead, M. (1950) *Quart. J. Child Behaviour*, 2, 237.
Newton, M., Newton, N. R. (1951) *Amer. J. Obstet. Gynec.* 61, 664.
Olmsted, R. W., Jackson, E. B. (1950) *Pediatrics*, 6, 396.
Waller, H. (1946) *Arch. Dis. Childh.* 21, 1.
— (1950a) *Lancet*, i, 53.
— (1950b) see *Brit. med. J.* ii, 351.
Walser, H. C. (1945) *Psychosomatic Med.* 7, 174.

THE SICKLE-CELL ANOMALY AS A SIGN OF MEDITERRANEAN ANÆMIA

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THE hæmolytic anæmia of the peoples of the eastern Mediterranean area has to be distinguished from that of the Negroes of Africa and America.

This problem arose when Cooley and Lee (1929), in the U.S.A., observed sick-cell anæmia and sickle-cell trait in a family of Greek immigrants from a village of Pyrgos, in the Peloponnesus, near Olympia. In this family 2 children, aged fourteen and four years, had hæmolytic anæmia and sickle-cell anomaly to a high degree, and their mother had incomplete development of sickle cells, but the father and the sister had neither. Cooley and Lee (1926) had previously described as a morbid entity an erythroblastic anæmia found in 5 patients, 2 of them being children of Greek immigrants, and the others Italians and Syrians.

Autochthonous cases of hæmolytic anæmia with sickle cells have since been reported in Greece (Caminopetros 1936, 1937a, 1938, 1949) and in Italy (Silvestroni 1949). Since the method of producing sickle cells in fresh sealed preparations of blood was generally adopted, the number of reports of cases of sickle-cell anomaly has been considerably increased in both countries (Comninos et al. 1950, Choremis et al. 1950, 1951, Vatsineas et al. 1952, Caminopetros et al. 1951b, Foy and Kondi 1951). But although more cases of sickle-cell anomaly are being reported in Greece, and therefore fewer cases of Cooley's erythroblastic anæmia, the former are nevertheless identified by most Italian and Greek pædiatricians with the sickle-cell anæmia of Negroes, to whom they consider that the sickle-cell anomaly is exclusively restricted.

PRESENT INVESTIGATION

The findings reported here indicate that the sickle-cell anomaly is common to the erythroblastic anæmia of white people and the hæmolytic anæmia of Negroes, the only difference being that it is manifested differently in these two conditions.

These findings concern two groups of patients and their apparently healthy relations, in whom the presence or absence of sickle cells was systematically and repeatedly investigated. The first group consists of patients from the village of Marcopoulo, in Attica, and the second of patients living in Athens but originating from villages or towns on the Greek mainland or islands.

Marcopoulo

The village of Marcopoulo (4000 inhabitants) and the neighbouring villages of Liopessi and Koropi were chosen for investigation so as to emphasise the fact that neither interbreeding with Negroes nor malaria and undernourishment contribute to the ætiology of this erythroblastic anæmia, as some Greek and Italian pædiatricians claim (Silvestroni 1949, Choremis et al. 1950, 1951, Choremis and Spiliopoulos 1936).

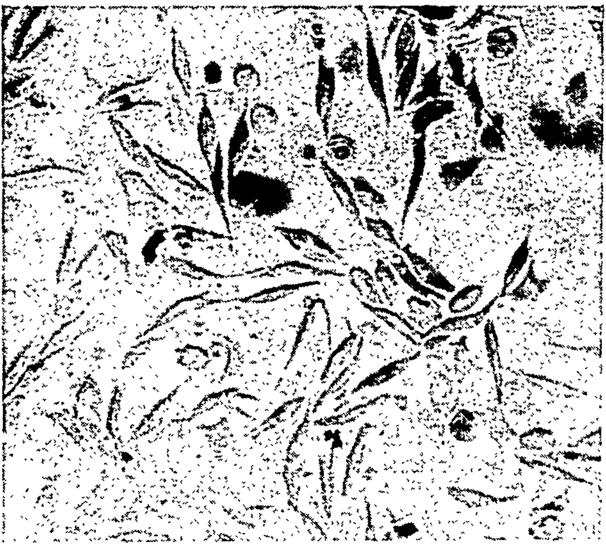

Fig. 1—Blood smear, showing "flagellate" sickle-cell cells and thin transparent cells starting to become sickle-shaped ("holly leaves," "stars"), from apparently healthy mother (table I, no. 33) of child with chronic anæmia, sickle cells, and cranial lesions (table I, no. 29).

In the vicinity of these villages of Mesogea in Attica malaria has never been endemic, and the inhabitants, being breeders of sheep, have better food than those of many other parts of Greece. Moreover they belong to the Illyrodinaric racial group, immigrated in the 14th century from the northern districts of continental Greece near Albania, and, so far as is known, they never interbred with Negroes.

The findings, some of which were communicated to the Medical Society of Athens (Caminopetros et al. 1951b), may be summarised as follows:

There were 7 families with 7 patients and 33 apparently healthy members (table I). The sickle-cell anomaly was found in 2 patients with chronic erythroblastic anæmia, one aged five and the other six years, but not in 2 patients, aged seven months and eight months, in families I and V with the severe acute von Jaksch-Luzet-Hayem form. The eight month child died a month after he had been examined; the other, when examined again, on Nov. 14, 1951, at the age fifteen months, had many sickle cells in one of four fresh preparations of blood.

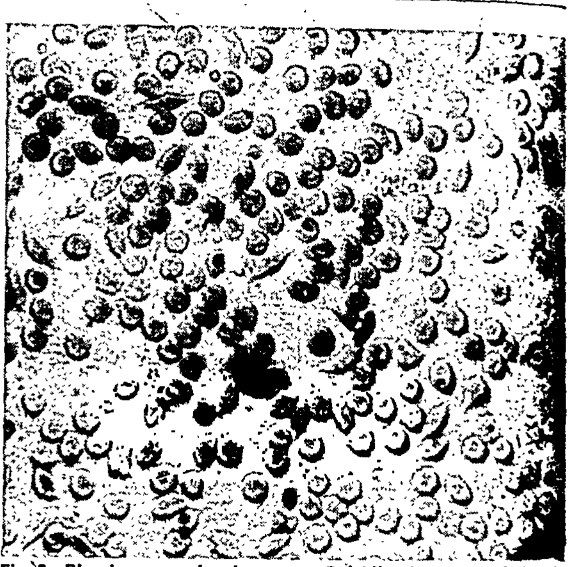

Fig. 2—Blood smear, showing start of sickling in apparently healthy brother (table I, no. 35) of girl with chronic anæmia and sickle cells (table I, no. 34).

Of the 33 apparently healthy persons in the 7 families, the sickle-cell anomaly was found in 25 (76%).

Athens

In the second group (table II) there were 18 families in which the sickle-cell anomaly was studied. The number of families affected by Cooley's erythroblastic anæmia that I have observed up to now, and which are spread all over Greece (insular and continental), is 141—37 families studied up to 1938, and a later group of 104, including the 18 families recorded in table II—the only families we could collect in Athens. From this table it will be seen that the sickle-cell anomaly was found in all 14 patients with chronic anæmia but in only 1 (no. 68) of the 6 infants with acute anæmia.

Of the 18 fathers 15 were examined for sickle-cell anomaly, and 13 of them were positive. Of the 18 mothers examined, 12 were positive. In 7 of the 18 families both parents were positive. Of 18 examined relations of the patients 12 were positive.

I should add that the fresh sealed preparations of blood, kept in the incubator at 32°C, were taken from the finger after it had been constricted with a rubber band for 30 minutes or more, the presence of sickle cells was checked in coloured dry smears of blood by the Giemsa or May-Grünwald method.

DISCUSSION OF FINDINGS

Incidence and Severity

In Cooley's erythroblastic anæmia, as in the erythroblastic anæmia of Negroes, the sickle-cell anomaly occurs more often in the chronic forms than in the acute forms seen in infants. In the latter this anomaly is manifested sometimes after the first year of age but is always incomplete (Watson et al. 1948, Singer et al. 1951).

The degree of the sickle-cell anomaly varies among the parents and other relations of the patients. If this anomaly happens to be of the highest degree in one of his parents or grandparents it is of the same degree also in the patient and definite enough in some of his siblings (family VIII, IX, XVI in table II). On the other hand, in the course of generations, the anomaly may be reduced to a lower degree, probably because of marriage with persons having it in a low degree (cf. family X in table II).

The sickle-cell anomaly may become so slight that, despite repeated examinations, only a few sickle cells are found in the fresh preparations. In dry smears many sickle cells are regularly found at the end of the smear and shaped like holly leaves, daisy leaves, or wine-skins, as often happens with leucocytes and with the big forms of *Plasmodium falciparum* or of *P. præcox*.

If the sickle-cell anomaly is of a low degree in both parents, the patients and the other descendants will have it also in a low degree.

The lower degree of sickle-cell anomaly can be easily recognised by the fact that the sickle cells usually appear after twelve hours, and then only in small numbers and in only one or two out of five or six fresh preparations.

When the anomaly is of high degree, all the red cells change into the fully developed "flagellate" sickle cells even without constriction of the finger and regardless of whether the person has the anæmia or is a carrier of the trait (family IX, mother and patient).

Physiognomy

The sickle-cell anomaly was observed in a patient with the most striking facies characteristic of chronic Cooley's erythroblastic anæmia—i.e., very advanced alterations of the bones of the face and skull, producing a monstrous appearance (Caminopetros 1937b) (fig. 7).

Negative Phase

An essential characteristic of the sickle-cell anomaly is the so-called negative phase, which is manifested by the disappearance of sickle cells in the fresh preparations of blood in patients as well as carriers. The negative phase occurs in periods of different duration and evidently constitutes an important obstacle in determining the presence or absence of sickle cells.

It is now clear that the mild cases of anæmia found among Negroes and Italians and diagnosed as Cooley's erythroblastic anæmia or trait (Dagradi et al. 1951, Schwartz and Mason 1949) because of the lack of sickle cells in the fresh preparations of their blood, in spite of the presence of such cells in the blood of their father (Powell et al. 1950), must be attributed to the negative phase.

The same explanation must be given for the exhibition of the sickle-cell anomaly by children while their parents are negative (Neel 1951).

Alterations in Vitro

The sickle cells, even those elongated ones with filamentous "flagella," usually revert, at the end of four or five days in vitro, to the discoidal form of normal red cells. This is probably due to saprophytes, sarcina, and *Corynebacterium cutis (communis)* which regularly grow in the fresh preparations of blood kept at 32°–35°C.

If fresh preparations of blood from a patient with sickle-cell anomaly of the highest degree or from a carrier of the trait of the same degree, in which all the red cells change in twelve hours to sickle cells, are kept afterwards in the refrigerator, the development of

TABLE I—SICKLE-CELL ANOMALY AT MARCOPOULO

No.	Person investigated (date in 1951)	Age	Red-cell fragility (% NaCl)	Clinical form of anæmia	Degree of sickle-cell anomaly in fresh preparation	Remarks
	Family I (March 12):					
1	Patient (male)	7 mos.	0·36–0·10	Acute	Nil on March 12	Sickle cells (D1) first found on Nov. 14, 1951, at age of 15 mos.
2	Father	36 yr.	0·38–0·24	..	D1	Anæmia in childhood without enlargement of spleen
3	Mother	30 yr.	0·36–0·20	..	D2	..
4	Brother	..	..	Acute	..	Died in 1949 aged 18 mos.
5	Paternal grandfather ..	66 yr.	..	..	Nil	..
6	Paternal grandmother ..	63 yr.	..	..	D2	..
7	Maternal grandfather ..	70 yr.	..	..	D1	..
8	Maternal grandmother ..	68 yr.	..	..	D1	..
9	Maternal uncle	28 yr.	..	..	D1	..
	Family II (March 12):					
10	Father (paternal uncle of no. 1)	39 yr.	..	..	Nil	..
11	Mother	36 yr.	..	..	D2	..
12	Daughter	6 yr.	0·38–0·20	Chronic	D2	Symmetrical enlargement of parietal bones
13	Son	9 yr.	..	..	Nil	..
14	Paternal aunt	28 yr.	..	..	D2	..
	Family III (March 12):					
15	Mother (paternal aunt of no. 1)	37 yr.	..	..	D1	..
16	Father	40 yr.	..	..	D1	..
17	Son	13 yr.	..	..	D1	..
18	Son	6 yr.	..	..	Nil	..
	Family IV (March 12):					
19	Mother (maternal aunt of no. 1)	43 yr.	..	..	D1	..
20	Daughter	15 yr.	..	..	D1	..
	Family V (June 12):					
21	Patient (female)	8 mos.	..	Acute	Nil	Died aged 10 mos.
22	Brother	7 yr.	..	..	D1	..
23	Sister	4 yr.	..	..	Nil	..
24	Father	39 yr.	..	..	D2	..
25	Mother	28 yr.	..	..	D2	..
26	Maternal grandfather ..	52 yr.	..	..	D1	..
27	Maternal grandmother ..	50 yr.	..	..	D1	..
28	Maternal aunt	23 yr.	..	..	D1	Anæmia in childhood
	Family VI (May 6):					
29	Patient (male)	5 yr.	..	Chronic	D2	Lesions of skull
30	Sister	..	..	Chronic	..	Died aged 5 yr. in 1943
31	Brother	17 mos.	..	..	Nil	..
32	Father	40 yr.	..	..	D1	..
33	Mother	30 yr.	..	..	D4	See fig. 1
	Family VII (May 27):					
34	Patient (female)	..	0·36–0·24	Chronic	D2	Died aged 8 yr. in 1947
35	Twins { Brother	6 yr.	0·34–0·22	..	D1	See fig. 2
36	Twins { Brother	6 yr.	0·38–0·22	..	D2	..
37	Father	44 yr.	0·36–0·24	..	D4	Anæmia in childhood, with enlarged liver and spleen; recovered at age of 7 yr.
38	Mother	39 yr.	0·38–0·28	..	D1	..
39	Maternal grandmother ..	65 yr.	..	..	Nil	..
40	Maternal grandfather ..	72 yr.	..	..	Nil	..

D1 = Few sickle cells in only 1 of 4 fresh preparations of blood.
D2 = Many sickle cells in 2 out of 4 fresh preparations.
D3 = A large number of red cells changed to sickle cells in 3 out of 4 fresh preparations.
D4 = All red cells changed to sickle cells in all 6 fresh preparations.

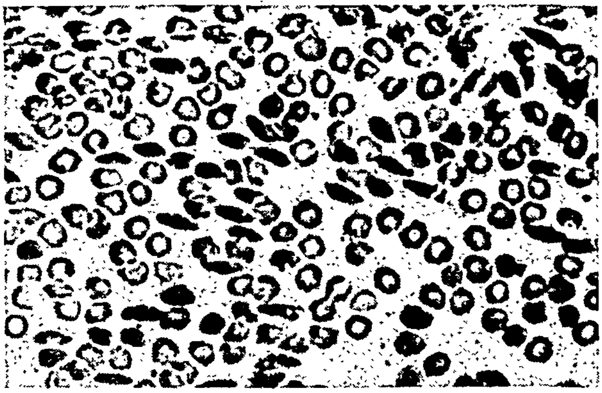

Fig. 3—Blood smear, showing sickle cells (" daisy leaves ") and target cells, from father (table II, no. 42), apparently spontaneously cured of chronic anæmia in childhood, of boy (table II, no. 41) with chronic anæmia, sickle cells, and advanced cranial lesions.

bacteria is prevented, and the sickle-cells, once formed, remain unaltered.

The thin and transparent red cells of macrocyte type which characterise the carriers of mild forms of sickle-trait (Smith 1943) seem to represent the first stage of sickle cells, because in the severe form in infants and in the chronic form these thin cells are few, and in wet

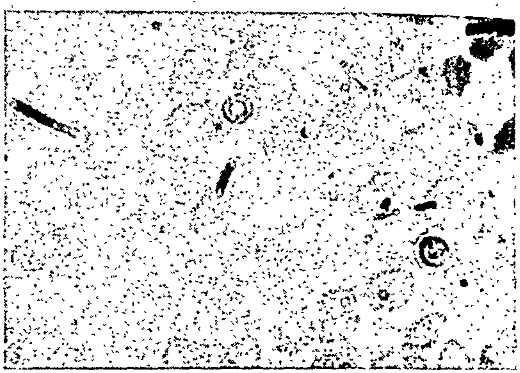

Fig. 4—Blood smear, showing sickle cells (" daisy leaves " and " oat cells "), from apparently healthy mother (table II, no. 48) of girl with chronic anæmia and sickle cells (table II, no. 46).

preparations it is easy to observe the various intermediate stages of their transformation to sickle cells. They contrast well with the very fragmented sickle-cell red cells.

In chronic anæmia and sickle-cell trait, both exhibiting the sickle-cell anomaly in fresh preparations in its most perfect manifestation, all the red cells change to " flagellate " forms. In dry smears, on the other hand, t change is limited to a few red cells, which are found at

TABLE II—SICKLE-CELL ANOMALY IN ATHENS

No.	Person investigated	Age	Origin	Red-cell fragility (% NaCl)	Clinical form of anæmia	Degree of sickle-cell anomaly in fresh preparations	Remarks
	Family VIII :						
41	Patient (male) ..	18 yr.	Psahna, Eubea Island	0·28–0·16	Chronic	D4	Advanced cranial lesions (fig. 10)
42	Father	58 yr.	,,	0·34–0·24	Chronic	D4	See figs. 3 and 11. Manifest anæmia in childhood followed by spontaneous cure at age of 8 yr.
43	Mother	45 yr.	,,	0·40–0·28	..	Nil	..
44	Paternal aunt ..	55 yr.	,,	0·42–0·30	..	D3	..
45	Paternal uncle ..	45 yr.	,,	..	..	D3	..
	Family IX :						
46	Patient (female) ..	14 yr.	..	0·36–0·22	Chronic	D4	Epistaxes
47	Father	45 yr.	Peloponnesus	0·40–0·20	..	Nil	..
48	Mother	35 yr.	Zihni, Asia Minor	0·40–0·20	..	D4	See fig. 4
49	Brother	16 yr.	,,	0·38–0·26	..	D2	..
50	Maternal grandmother	70 yr.	,,	0·38–0·20	..	D4	..
51	Maternal grandfather	72 yr.	,,	0·40–0·24	..	Nil	..
	Family X :						
52	Patient (male) ..	14 yr.	..	0·38–0·20	Chronic	D1	Spontaneous clinical cure 3 years ago; radiography shows advanced cranial lesions
52A	Father..	40 yr.	..	0·46–0·32	..	Nil	..
53	Brother	16 yr.	..	0·38–0·20	..	D1	..
54	Mother	34 yr.	Zihni, Asia Minor.	0·36–0·20	..	D2	Maternal aunt of family IX
	Family XI :						
55	Patient (male) ..	24 mos.	Strefi (Pylia), Peloponnesus	0·38–0·10	Acute	Nil	A brother with acute anæmia died last year
56	Father	38 yr.	..	0·40–0·24	..	Nil	..
57	Mother	37 yr.	,,	0·36–0·22	..	D3	..
58	Maternal uncle ..	28 yr.	,,	0·38–0·20	..	D2	..
59	Maternal aunt ..	40 yr.	,,	0·38–0·22	..	D2	..
	Family XII :						
60	Patient (male) ..	11 yr.	..	0·38–0·22	Chronic	D2	Parietal bones thick and prominently enlarged
61	Father	33 yr.	Pylia, Peloponnesus	0·38–0·20	..	D2	Yellow skin
62	Mother	36 yr.	Lamia (continental Greece)	0·42–0·28	..	Nil	..
63	Sister	6 yr.	..	0·40–0·26	..	Nil	..
	Family XIII :						
64	Patient (female) ..	13 yr.	..	0·40–0·18	Chronic	D4	See figs. 5 and 6. Splenectomy in 1947; a sister died of anæmia at age of 9½ yr.
65	Father	..	Gythion, Peloponnesus	0·40–0·26	..	D4	Anæmia manifest in childhood, followed by spontaneous recovery at age of 9 yr.
66	Mother	..	,,	0·38–0·24	..	Nil	..
67	Sister	16 yr.	..	0·42–0·28	..	D4	..
	Family XIV :						
68	Patient (female) ..	22 mos.	Epirus	0·36–0·14	Acute	D2	..
69	Father	..	,,	0·36–0·20	..	D2	..
70	Mother	..	,,	0·36–0·20	..	D2	..
71	Maternal grandmother	..	,,	0·38–0·20	..	D3	..
	Family XV :						
72	Patient (female) ..	14 yr.	..	0·38–0·26	Chronic	D1	Epistaxes; died Oct. 23, 1951
73	Father	..	Meligala, Peloponnesus	0·42–0·30	..	D1	..
74	Mother	..	Smyrna, Asia Minor	0·40–0·22	..	D2	..
75	Brother	11 yr.	..	0·44–0·28	..	D1	..

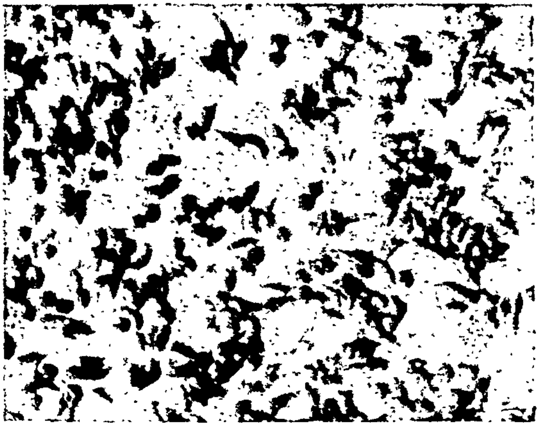

Fig. 5—Blood smear, showing early stage of sickling (after six hours), from girl (table II, no. 64) with chronic anæmia who had undergone splenectomy.

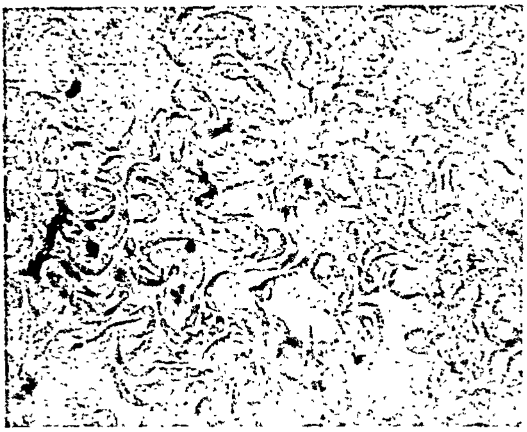

Fig. 6—Blood smear from same patient as in fig. 5, showing full development of sickle cells.

the edge of the end of the smear, while nearly all the other red cells take the form of target cells.

Another remarkable fact is that these sickle cells, despite their small number, are constantly found in the dry smears, even in the negative phase (see above), which is often observed in fresh preparations.

The sickle cells in dry smears are usually shaped like daisy leaves; but sometimes like pencils or spindles ("oat cells"), as in fig. 2.

These sickle cells, especially in carriers of the sickle-cell anomaly, are often taken for artefacts because of their localisation at the edges of the smears; but this localisa-

TABLE II—*continued*

No.	Person investigated	Age	Origin	Red-cell fragility (% NaCl)	Clinical form of anæmia	Degree of sickle-cell anomaly in fresh preparations	Remarks
	Family XVI:						
76	Patient (female) ..	28 yr.	Poros Island	0·34–0·22	Chronic	D4	Three brothers apparently healthy
77	Father	62 yr.	”	0·42–0·32	..	D1	..
78	Mother	48 yr.	”	0·30–0·18	Chronic	D4	Anæmia; spleen and liver not enlarged; bone lesions very pronounced
79	First cousin	22 yr.	”	..	..	D2	..
80	Brother	30 yr.	”	..	..	Nil	..
	Family XVII:						
81	Patient (male) ..	16 yr.	Corfu Island	0·38–0·20	Chronic	D1	Advanced lesions of bones of skull and upper jaw (figs. 7 and 12), typical case of Cooley's anæmia, ulcers of legs
82	Father	..	”	0·34–0·20	..	D1	..
83	Mother	..	”	0·38–0·24	..	D1	..
84	Maternal aunt ..	..	”	0·40–0·24	..	Nil	..
	Family XVIII:						
85	Patient (male) ..	20 yr.	..	0·36–0·18	Chronic	D1	..
86	Father	..	Istambul, Turkey	0·40–0·30	..	D1	..
87	Mother	..	Kea Island	0·38–0·24	..	D1	..
88	Maternal aunt ..	..	”	0·38–0·26	..	Nil	..
	Family XIX:						
89	Patient (male) ..	22 yr.	..	0·32–0·20	Chronic	D4	Large ulcers of legs (fig. 8) for 4 yr.
90	Father	64 yr.	Crete	0·34–0·21	..	D4	..
91	Mother	54 yr.	Kiurka, Attica	0·40–0·22	..	Nil	..
92	Brother	30 yr.	..	0·40–0·30	..	Nil	..
93	Brother	24 yr.	..	0·36–0·22	..	Nil	..
	Family XX:						
94	Patient (female) ..	16 yr.	..	0·35–0·25	Chronic	D2	..
95	Father	..	Samos Island	..	..	..	Not examined
96	Mother	38 yr.	Iconieh, Asia Minor	0·44–0·35	..	D1	..
	Family XXI:						
97	Patient (male) ..	17 mos.	..	..	Acute	Nil	Died Feb. 2, 1951
98	Father	..	Adalia, Asia Minor	0·40–0·26	..	D1	..
99	Mother	..	”	0·38–0·22	..	Nil	..
	Family XXII:						
100	Patient (male) ..	11 mos.	..	0·36–0·20	Acute	Nil	Died in 1947 at age of 11 mos.
101	Father	30 yr.	Smyrna } Asia Minor	0·38–0·24	..	D1	..
102	Mother	29 yr.	Alaya	0·38–0·24	..	Nil	Maternal aunt of family xiv
	Family XXIII:						
103	Patient (male) ..	12 mos.	..	0·42–0·22	Acute	Nil	Died January, 1950, at age of 14 mos.
104	Father	27 yr.	Smyrna, Asia Minor	0·30–0·26	..	D2	..
105	Mother	30 yr.	Carystos, Eubea Island	0·42–0·30	..	D1	..
	Family XXIV:						
106	Patient (male) ..	4 mos.	..	0·35–0·20	Acute	Nil	Died. Another sibling had severe anæmia
107	Father	30 yr.	Island of Zante	0·35–0·20	..	D2	..
108	Mother	23 yr.	Armenia Asia Minor	0·38–0·22	..	D2	..
109	Maternal grandmother	..	”	0·40–0·22	..	D2	..
	Family XXV:						
110	Patient (male) ..	12 yr.	Psahna, Eubea Island	0·38–0·20	Chronic	D4	See fig. 9. Father killed in war
111	Mother	..	”	..	..	D4	Anæmia cured in childhood at age of 9 yr.

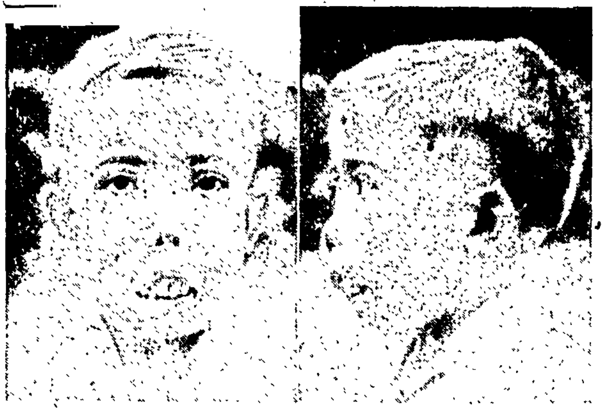

Fig. 7—Boy (table II, no. 81), aged 16, with chronic anæmia, sickle cells, crural ulcers, and advanced lesions of bones of skull and upper jaw.

tion is due to their large size, as happens with large plasmodia or leucocytes.

Red-cell Fragility

The decrease of red-cell fragility, which is an essential element of erythroblastic anæmia and its trait (Caminopetros 1936) was found to be proportional to the severity of the sickle-cell anomaly in the carriers as well as in the patients. The only exception was in the acute fatal anæmia of early infancy, in which, though the sickle-cell anomaly is often absent, the red-cell fragility is at its lowest. The reasons for the low fragility seen in infancy are probably the accentuated fragmentation of the erythrocytes and the abnormal hæmoglobin of the newborn.

Spontaneous Cure

Some of the parents examined gave a history of severe anæmia during their childhood, but had recovered gradually to such an extent that they may now be considered as clinically cured—e.g., father of family VIII, father of family XIII, mother of family XXV (table II), and father of family VII (table I). Such a spontaneous cure was seen also in the patient of family X (table II) now aged fourteen. He had severe erythroblastic anæmia up to the age of eleven, but later the enlargement of his spleen and liver and the pallor of his skin disappeared completely, and he only retained the advanced lesions of his skull and the sickle-cell trait; in other words, he became only a carrier.

Ethnical Differences

The sickle-cell anomaly was found in 49·1% of the population of Athens—i.e., a higher incidence than among Negroes (Powell et al. 1950, Neel 1951, Abassy 1951). But it was of a much lower degree than in Negroes; for, as a rule, of every four to six fresh blood preparations examined only one was positive. Examining 116 Athens adults originating from different areas of the Greek [illegible] people [illegible] Minor) [illegible] In addition the investigation was extended to gipsies settled in Athens, because 2 cases of acute sickle-cell anæmia had previously been found in 2 families (Caminopetros et al. 1951a). In the present investigation, out of 26 gipsies examined 12 (46%) were carriers of the sickle-cell anomaly. This group of gipsies, as well as those who are wandering round Macedonia and Thessaly, often interbreed with Greeks. Thus, our second gipsy patient with erythroblastic anæmia had a father who was pure gipsy, married to a Greek from the Peloponnesus.

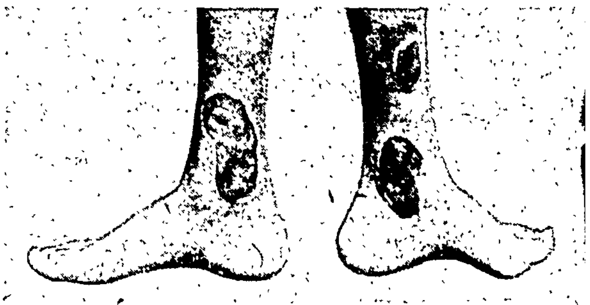

Fig. 8—Crural ulcers of man, aged 22, with chronic anæmia and sickle cells (table II, no. 89).

The erythroblastic anæmia is not concentrated in certain foci in Greece but is widespread over the mainland and the islands, as proved by local surveys made since 1937 in different provinces of Crete, of the Peloponnesus (the villages of Messinia plain), in continental Greece (Livadia, Thebes, &c.), and in the island of Corfu. In all the villages the incidence of the erythroblastic anæmia is reasonably uniform (about 6–10 affected families in every village of 2000–4000 inhabitants).

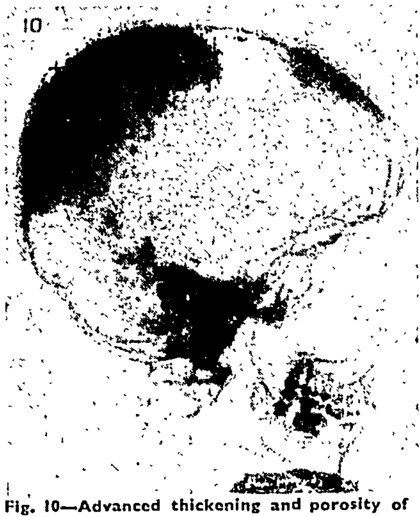

Fig. 10—Advanced thickening and porosity of cranial bones, with enlargement of parietal bones to form a hump, in boy with chronic anæmia and sickle cells (table II, no. 41).

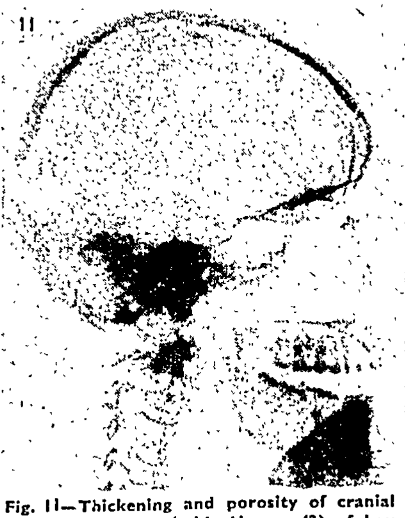

Fig. 11—Thickening and porosity of cranial vault in father (table II, no. 42) of boy whose cranial lesions are shown in fig. 10.

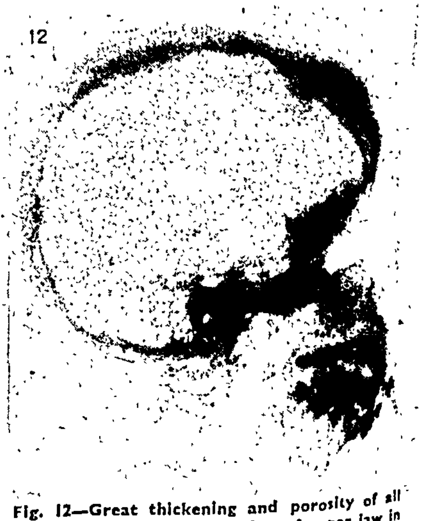

Fig. 12—Great thickening and porosity of all cranial bones and protrusion of upper jaw in same patient as in fig. 7.

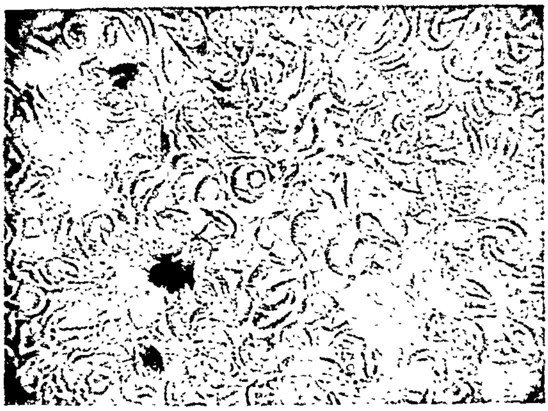

Fig. 9—Blood smear, showing "flagellate" sickle cells, from boy with chronic anæmia (table II, no. 110).

The erythroblastic anæmia is connected especially with certain racial groups (Alpine Illyrodinaric) which are prevalent in Greece and in Southern Italy (Caminopetros 1938, Chini 1939, Chini and Malaguzzi Valeri 1949). Many cases of erythroblastic anæmia, both acute and chronic, have also been observed among Armenian refugees from Asia Minor (Alpine Armenoid racial type). Chronic erythroblastic anæmia has been observed in Turkey (in Asia Minor (Fakacelli 1947) and in China it seems to be not uncommon (DeMarsh 1950)).

The erythroblastic anæmia does not affect the real Mediterranean racial type, or the nomad shepherds of Mount Pindos (Sarakatsaneï), in whom neither the eyes nor any other bodily characters show mongoloid elements. It is the Alpine, Illyrodinaric, and Armenoid racial groups (now forming a large majority of the population of Greece) that are exclusively affected by erythroblastic anæmia; and in these a mongoloid facies is apparent even in individuals free from the anæmia (Atkinson 1939). These groups represent stocks which, often early in history, invaded Greece from Asia, either from the Carpathians or from Asia Minor (Deniker 1926, Pittard 1916, Hooton 1939, Montagu 1945, Angel 1946, Lambros 1902, Amantos 1923, 1947, Zacynthinos 1945, Keramopoulos 1945).

SUMMARY AND CONCLUSIONS

The sickle-cell anomaly is not peculiar to Negroes but is also a feature of the erythroblastic anæmia of white people. Therefore the sickle-cell anomaly must be added to the characteristics which have already been recognised as common to both forms of anæmia—e.g., target cells, ulcers on the legs, lesions of the skull, and decreased fragility of the red cells.

In spite of the important similarities between these two anæmias, there are also some significant discrepancies —e.g., the low degree of sickle-cell anomaly in the apparently healthy members of the families of patients as well as in the population of Greece. Hence we must regard these anæmias as two distinct morbid entities.

The erythroblastic anæmia in the white races is probably due to the admixture of mongol blood during the march from Asia towards the West. We cannot attribute the appearance of the erythroblastic anæmia to a racial mixing between Negroes and the Mediterranean groups. The fact that the erythroblastic anæmia connected with sickle-cell anomaly is uniformly widespread in the villages and towns of continental and insular Greece disproves the theory of an admixture with Negro blood. If there had been such an admixture, there would also be other Negro physical characteristics present.

In view of the present findings I suggest that the terms "erythroblastic anæmia," "Mediterranean anæmia," and "thalassæmia" be superseded by the more accurate term "drepanocytic anæmia of the Eastern Mediterranean."

REFERENCES

Abassy, A. S. (1951) *Blood*, 6, 555.
Amantos, C. (1923) The Northern Neighbours of Greece. Athens.
— (1947) History of Byzance. Athens.
Angel, J. L. (1946) *Hum. Biol.* 18, 1.
Atkinson, D. W. (1939) *Amer. J. med. Sci.* 198, 376.
Caminopetros, J. (1936) *C.R. Soc. méd. Athènes*, Jan. 18, p. 11.
— (1937a) L'anémie érythroblastique des peuples de la Méditerranée orientale. Published by the Academy of Athens.
— (1937b) *Bull. Soc. méd. Hôp. Paris*, 53, 1442.
— (1938) *Ann. Méd.* 43, 104.
— (1949) *Congr. int. Path. comp.* Istambul (in the press).
— Mazidis, S., Stavridhis, J. (1951a) *C.R. Soc. méd. Athènes* Feb. 10, p. 82.
— — — (1951b) *Ibid.* March 31, p. 196.
Chini, V. (1939) *Policlinico*, sez. prat. 46, 671.
— Malaguzzi Valeri, C. (1949) *Blood*, 4, 989.
Choremis, C., Spiliopoulos, I. (1936) *Iatr. Chron.* February, p. 83.
— Zervos, N., Constantinidis, V., Zannou, L. (1950) *C.R. Soc. méd. Athènes*, Nov. 11, p. 472.
— — — — (1951) *Lancet*, i, 1147.
Cómninos, D., Bacalos, D., Catsiroumbas, P. (1950) *C.R. Soc. méd. Athènes*, April 1, p. 154; Nov. 4, p. 435.
Cooley, T. B., Lee, P. (1926) American Pediatric Society, Niagara Falls; American Medical Association.
— — (1929) *Amer. J. Dis. Child.* 38, 103.
Dagradi, A. E., Sollod, N., Friedlander, J. H. (1951) *J. Amer. med. Ass.* 145, 317.
Deniker, J. (1926) Les races et les peuples de la terre. Paris.
DeMarsh, Q. B. (1950) *Blood*, 5, 798.
Fakacelli, N. M. (1947) *Türk tip cem. mec.* 13, 238.
Foy, H., Kondi, A. (1951) *Lancet*, ii, 451.
Hooton, E. A. (1939) Twilight of Man. New York.
Keramopoulos, A. (1945) The Greeks and the Northern Neighbours. Athens.
Lambros, S. (1902) History of Greece. Athens.
Montagu, M. F. A. (1945) An Introduction to Physical Anthropology. Springfield, Ill.
Neel, J. V. (1951) *Blood*, 6, 389.
Pittard, E. (1916) Les peuples des Balkans. Neuchâtel.
Powell, W. N., Rodarte, J. G., Neel, J. V. (1950) *Blood*, 5, 887.
Schwartz, S. O., Mason, J. (1949) *Ibid*, 4, 706.
Silvestroni, E. (1949) *Congr. Soc. ital. Med. intern.* Rome.
Singer, K., Chernoff, A. I., Singer, L. (1951) *Blood*, 6, 429.
Smith, C. H. (1943) *Amer. J. Dis. Child.* 65, 681.
Vatsineas, P., Pouliacos, P., Apostolidis, A. (1952) *C.R. Soc. med.-chir. Athènes* (in the press).
Watson, J., Stahman, A. W., Bilello, F. P. (1948) *Amer. J. med. Sci.* 215, 419.
Zacynthinos, D. (1945) The Slaves in Greece. Athens.

HYPERTHYROIDISM AND PEPTIC ULCER

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The simultaneous occurrence of hyperthyroidism and active peptic ulceration seems to be rare. Garbat (1951) points out that such a combination could be expected more frequently, since both diseases are common, both are associated with stress, and both have an election for young adults and a tendency to chronicity and relapse. He remarks that other workers have noted how rarely the two diseases are associated and have explained this by postulating a nervous balance whereby, when vagal tone is decreased, there is compensatory sympathetic hypertonus, and vice versa. In peptic ulcer vagal tone is increased, whereas in hyperthyroidism there is sympathetic hypertonus; according to the nervous-balance theory these states cannot occur together. Garbat prefers the conception of a disharmony of the vegetative nervous system, this idea being supported by the findings, in some of his cases, of a raised basal metabolic rate (B.M.R.) associated with a normal or slow pulse-rate and gastric hypersecretion. In ten years he found only 6 cases of hyperthyroidism associated with an active ulcer: 2 in his hospital and 4 in his private practice. Of the latter, 1 patient improved on medical treatment, 1 underwent both partial gastrectomy and partial thyroidectomy, and 2 recovered after partial thyroidectomy alone. Jackson (1949) observed that a high proportion of patients with peptic ulcer showed lid lag, and he cited Eason (1927) as saying that this sign is not peculiar to thyrotoxicosis, and Joll (1932) that it may occur in normal people. Jackson investigated the incidence of lid lag in people without thyroid disease and noted it in 33% of ulcer cases and in 10% of his controls. It was more common in thin people and in males, thus perhaps accounting for his findings.

During the course of a year, out of a total of some 130 cases of peptic ulcer, we have seen 3 patients with associated hyperthyroidism. This unusually high incidence has led us to record a brief summary of each case.

CASE-RECORDS

Case 1.—A labourer, aged 35, was known to have had a gastric ulcer for eight years. Besides his ulcer symptoms, he had nervousness, loss of weight, sweating, tachycardia and exophthalmos, and his B.M.R. was +25%. Gastroscopy revealed two active lesser-curve ulcers. He was put to bed on routine ulcer régime and given thiouracil. On his discharge six weeks later the B.M.R. was normal and he had gained 7 lb. in weight. Repeat gastroscopy showed that both ulcers had healed. Seen again six months later, he was still well, taking a daily maintenance dose of thiouracil.

Case 2.—A car-park attendant, aged 44, was known to have had a duodenal ulcer for two years. In addition he had lassitude, nervousness, shortness of breath, tachycardia, and tremor; his pulse-pressure was raised and his B.M.R. was +74%. Radiography showed an ulcer crater in the duodenum. He was given routine ulcer treatment and thiouracil, and kept in bed. In the first few weeks he improved considerably, but in time he became intolerant to thiouracil, which nauseated him so that eventually it had to be abandoned. Gradually the symptoms and signs of hyperthyroidism and duodenal ulceration returned, and three months after admission partial thyroidectomy was performed. Four weeks later he was discharged, symptom-free, and with B.M.R. normal; radiography with barium meal showed a scarred duodenal cap. He was well when seen six months later.

Case 3.—A fruit merchant, aged 38, was known to have had a duodenal ulcer for seven years. Apart from his ulcer symptoms he had nervousness, sweating, and tachycardia, and his B.M.R. was +70%. Radiography showed a duodenal ulcer crater. He responded well to medical treatment, including thiouracil, and his B.M.R. returned to normal. He was symptom-free when, three months later, a partial gastrectomy was performed. At operation scarring of the duodenal cap was found. He continued to take a maintenance dose of thiouracil and remained well nine months later.

Further follow-up of these cases has unfortunately not been possible, because Stoke Mandeville Hospital is no longer under the control of the Ministry of Pensions, and the gastric unit has therefore closed down.

Our thanks are due to the Director-General, Medical Services, Ministry of Pensions, for permission to publish; to Mr. Harold Burge for the thyroid and gastric surgery; and to Dr. Spalding Smith for the radiology.

REFERENCES

Eason, J. (1927) Exophthalmic Goitre. Edinburgh.
Garbat, A. C. (1951) *J. Mt Sinai Hosp.* 17, 787.
Jackson, W. P. U. (1949) *Brit. med. J.* ii, 847.
Joll, C. A. (1932) Diseases of the Thyroid Gland. London.

"... Admission to an institution which caters for patients suffering from the same complaint has its advantages and disadvantages. On the one hand, as far as the patient is concerned, it does away with the feeling that he is one of the few unlucky ones; on the other, it brings him face to face with the worst features of his complaint, with complications, with setbacks and failures of treatment. Patients are inclined to compare notes and, according to their temperament, they may either derive comfort from those who recovered or be thrown into despair by those who did badly. Generally speaking, it is true that hearty, outgoing individuals revel in the community life of the ward, whereas shy, retiring, shut-in individuals suffer acutely under the same circumstances. One may well wonder whether, and how often, the beneficial effect of institutional care is cancelled by the misery of these patients and whether selection of patients for institutional care, if based not only on physical grounds but also on an assessment of the personalities concerned, would not pay a high dividend."
—E. WITTKOWER, *Canad. med. Ass. J.* 1952, 66, 220.

FAMILIAL CATARACT AND MENTAL DEFICIENCY

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A FAMILIAL incidence of cataract has often b observed, both in man and animals, and the condit is commonly attributed to a dominant gene. Ind Ford (1948) lists congenital cataract as due to a sin dominant. Though such oversimplification may be d cult to avoid in a short textbook for students, it r have the effect of encouraging irresponsible enthusi for eugenics.

The potential causes of cataract at any age are mult and are both genetic and environmental. Grunel (1947) points out that in the rat with degeneratio the retina cataract is a secondary phenomenon a possible photochemical basis. A similar interac between genetic and environmental factors is obviou cataract with aniridia. Many of the cases of this condi cited by Bell (1932) developed the cataract at a relati late stage, and again a photochemical action is probable explanation of the poor vision (Alger 194 this condition.

The study of maternal rubella has thrown light environmental factors which may produce conge cataract with associated anomalies (Gregg 1941). therefore now opportune to re-examine in the ligh this new knowledge those cases of congenital cata in which no ætiological factor is apparent.

The following case is distinguished by the associa in the affected members of the family of a brain le (as shown by mental deficiency) with the conge cataract.

CASE-RECORD

A girl, aged 7 years, was admitted in 1947. She had wei at birth 5 lb. 12 oz. The birth was said to be normal, and t was no jaundice. Bilateral nuclear cataract and strabis were noted soon after birth. At the age of 10 months infant attended hospital for treatment for talipes equi and later she attended on several occasions for needling cataract in the right eye. She was not brought for needlin the left lens as arranged.

Family History (see figure)

The patient's father is a labourer, often out of work thro disagreement with his employer, and is said to steal and t often in trouble with the police. He is a heavy drinker has been treated for gonorrhœa. The mother does dom work and has a bilateral congenital cataract which needled at Bath Eye Infirmary. She has been in prison, been treated for gonorrhœa, and is of poor intelligence. was one of twelve siblings, of whom four died in early infa The father was aged 23 at the birth of the patient, mother 21.

The patient is the first of three children, the secon whom, a boy, is enuretic and educationally backward attends a normal school. The third child, who has the s mother but whose father was a member of the U.S.A. Fo was born in Cardiff Prison Hospital in 1944. She, too, h bilateral congenital nuclear cataract, and she is educatio backward.

The maternal grandfather had a bilateral cataract. maternal grandmother is said to have died of diabetes. maternal uncle was in a mental-deficiency institution died while out on licence. He had no cataract, his visio both eyes being 6/6. A maternal aunt was epileptic, another died of a stroke.

The mother married when she was 6 months pregnant did not attend the antenatal department until the 5th mo She states that she now needs treatment for gonorrhœa. home is described as very poor, dirty, and with little furnit

Condition and Progress

On admission in 1947 the patient could not talk intellige and was doubly incontinent, nervous, and timid.

In 1949 she gave her name and age correctly, described adequately what she did in class, and counted parrot fashion, but she could not add 2 and 2, and could not spell. She could only scribble with a pencil, although she seemed to have a fair degree of vision and could name primary colours. She could obey simple commands and did little things for herself. She washed, fed, and dressed herself with help. Physically she was thin, and walked with a limp; the muscles of the left calf were wasted, and there was an operation scar. She could see a torch held in front of her eyes and followed it with nystagmoid movements. There was a bilateral cataract, the right pupil was bound down, and the left pupil was sluggish in its reaction to light. There were alternating internal strabismus and nystagmus.

In 1951 she scored an I.Q. of 49 on the Langan adaptation of the Binet test. She appeared just below the borderline of educability but responded well to training and seemed likely to make further improvement. A Wassermann test and a Meinicke reaction were negative. A tuberculin test was negative before vaccination with vole tubercle bacilli.

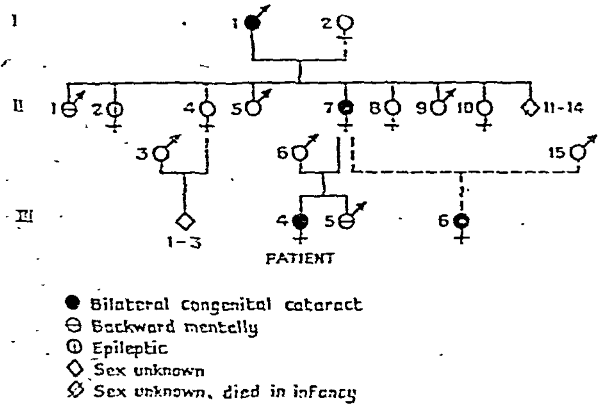
In September, 1951, Mr. L. H. Savin reported as follows: "The child has pendulum nystagmus in both eyes, presumably due to faulty development of macular vision in early life. She has a left divergent squint of 20°, and there is gross overaction of the left inferior oblique muscle. The right eye is aphakic but has been left with an opaque lens capsule. The left eye is also aphakic, but there is a large mass of lens debris. It is impossible at this stage to say very much about the type of cataract the child originally had, as the picture is quite altered by previous operative procedures."

Electro-encephalography

Dr. D. A. Pond reported on an electro-encephalogram taken on July 12, 1951, as follows: "In the posterior regions some alpha activity could be seen when the eyes were closed, but slower activity was present in equal amounts. The frontal and central regions were occupied by fairly high-voltage beta rhythm at 18–20 cycles per sec., which was symmetrical and unaffected by eye opening and shutting. All the activity appeared symmetrical. The changes are suggestive of some diffuse organic disturbance affecting the posterior regions least. As beta rhythm is uncommon and of unknown physiological significance, it would be of interest to see whether there is a familial resemblance of E.E.G. in view of the likeness of the clinical condition in members of the family."

Urine

A glucose-tolerance curve was of the "lag-storage" type, returning to well below normal in $2\frac{1}{2}$ hours. Chromatographic investigation showed the urinary excretion of amino-acids to be normal. The urine contained no galactose but about 30 mg. of glucose per 100 ml. A galactose-tolerance test on July 23, 1951, showed 2·2 g. (normal 0–3 g.) of galactose excreted. A test for phenylketonuria was negative.



Family tree showing inheritance of cataract:

I. 1, bilateral cataract, labourer, often out of work;
  2, died of diabetes;

II. 1, mental deficiency (normal vision);
  2, epileptic, ordinary school;
  4, died of heart attack, 3 children ordinary school;
  5, married, ordinary school;
  6, alcoholism, bad temper, gonorrhœa;
  7, bilateral cataract, strabismus, poor intelligence, prostitute;
  8, died of stroke, ordinary school;
  9, married, ordinary school;
  10, married, ordinary school;
  11–14, died in very early infancy, position in family unknown;
  15, in American forces;

III. 4, bilateral cataract;
  5, enuretic, educationally backward;
  6, bilateral cataract, strabismus, educationally backward, born in prison.

DISCUSSION

Duke-Elder's (1934) dictum may still be correct—namely, that "a large number of types of congenital cataract exist, the differentiation of which, from the practitioner's point of view with regard to heredity, is not of fundamental importance." But further developments in medical knowledge may make the differentiation of the genetic and environmental factors which produce the group of conditions described as "congenital cataract" of immediate practical importance. If, for example, cataract and brain damage are due to galactose intolerance, the baby so affected should be weaned and given a lactose-free diet at the first possible moment.

In the present case the absence of definite neurological lesions, except squint and talipes, and the presence of feeble-mindedness, suggest a diffuse brain lesion associated with the cataract. In most of the published cases of congenital cataract little mention is made of the mental state, and it is probable that mental defect amounting to feeble-mindedness only would often escape attention. Knapp (1926), describing a family containing 19 patients with cataract, stated that all were of normal mentality. Harman (1909) noted that the intelligence of a family containing 10 members with cataract was "below average." Worth (1930) mentions that in some cases of congenital cataract there is a history of convulsions. Manson (1928) stated that out of 13 persons with lamellar cataract in one family 2 were mentally defective. Danforth (1914) spoke of the association of hereditary congenital cataract with nystagmus and "slight mental deficiency," but attributed the association to selective mating. In Saebo's (1949) material of 20 cases of congenital cataract 1 patient was an imbecile (born, however, to an eclamptic mother). Wilson (1940) held that the association of mental deficiency and dystrophia myotonica, in which condition fine cataracts may be the earliest manifestation, is fortuitous. In any event obvious cataracts are not present in this condition at birth. Another association of cataract and mental deficiency is found in mongolism (Lowe 1949). In this condition also gross cataract is not often present at birth and a familial incidence is rare. In the present case the features and build do not at all suggest mongolism.

Penrose (1949) points to the occasional association of cataract and mental defect as evidence of gene pleiotropism. This explanation would fit the facts in the present case in so far as the patient's maternal uncle who was certified as mentally defective did not have a cataract. Indeed it is well recognised that, if hereditary traits are to be transmitted in a dominant manner at all, there must be considerable variation in their manifestation. As the present family tree shows, cataract in itself does not prevent marriage and reproduction. It is, however, unlikely that the patient will herself produce children, and it can be assumed that the degree of mental defect in those relations who have married and had children is appreciably less. A similar position obtains, as is well known, in epiloia, which has also been regarded as a "dominant" character but which is extremely variable in its manifestations. Thus, an idiot with fully developed epiloia is biologically and socially sterile, whereas a person with average intelligence and only a slight facial blemish of adenoma sebaceum may be an acceptable mate.

It is obvious, however, that such gene "pleiotropism" is not the only possible explanation for the occurrence in one family of different degrees of severity of the same syndrome. If the case of cataract produced by galactose intolerance (Goldstein and Ennis 1948) be taken as a parallel, it is clear that the amount of lactose in the diet will determine the severity of the lesion, thus emphasising the truth that what is inherited is not a character but merely a predisposition, the actual degree of realisation of which depends on environmental factors. Brolin and Krakau (1949) have shown that the occurrence of this type of cataract in rats is directly proportional to the percentage of galactose in the diet. It is, for example, probable that, in a case of galactose intolerance, if the infant receives no lactose at any time it may develop normally.

Thus we have travelled a long way from the position adopted by Gates (1929) when he said of congenital cataract, probably quoting Macklin (1927), that "there are many types all with strong evidence of inheritance." We now know that some cases are due to the action of the rubella virus during pregnancy (cases in which the genetic element is presumably unimportant): 5 such cases in the Fountain Hospital with a population of 650 are attributed to this factor. We have further the example of galactose intolerance to suggest that in the remaining cases environmental factors may be just as important as genetic. A static arrangement of the facts to fit preconceived genetic patterns in terms of "2 dominant and 3 recessive factors" leads to pessimism and therapeutic nihilism in the field of mental deficiency.

A chemical examination and reformulation of the data may be of great help in elucidating some of the problems in this field, may make therapy, if started early, worth while, and will at least render the practitioner better able to advise the parents of a defective child who consult him about the outcome of future pregnancies. Duke-Elder's (1943) statement still holds good that "the ætiology of these opacities depends upon some disturbance in the development of the lens, but what the actual disturbance may be, or the precise method of its action, is a matter of considerable doubt in most cases." It seems, however, reasonable to hope that, with a proper concentration of research on this problem, the nature and mode of action of the noxious factors may be understood in a considerable proportion of cases.

SUMMARY

A case of congenital familial bilateral cataract with imbecility (Langan I.Q. 49) is described. In three generations 4 persons were affected by cataract, a 5th by mental deficiency, and a 6th by epilepsy. A galactose-tolerance test gave negative results.

Our thanks are due to Dr. D. A. Pond for the report on the electro-encephalogram; to Dr. R. R. Race for the blood-groups; to Dr. L. I. Woolf for the biochemical reports and the interesting suggestion that galactose intolerance might be a causal factor; to Dr. W. W. Kay for the serological examinations; and to Mr. L. H. Savin for the report on the eyes.

REFERENCES

Alger, L. G. (1945) *Amer. J. Ophthal.* 28, 730.
Bell, J. (1932) Treasury of Human Inheritance. London; vol. II, part v, p. 527.
Brolin, S. E., Krakau, C. E. T. (1949) *Acta ophthal., Kbh.* 27, 291.
Danforth, C. H. (1914) *Amer. J. Ophthal.* 31, 161.
Duke-Elder, W. S. (1934) Chances of Morbid Inheritance. Edited by C. P. Blacker. London; p. 172.
— (1943) Textbook of Ophthalmology. London; p. 1356.
Ford, E. B. (1948) Genetics for Medical Students. London; p. 150.
Gates, R. R. (1929) Heredity in Man. London; p. 97.
Goldstein, E. O., Ennis, J. E. (1948) *J. Pediatr.* 33, 147.
Gregg, N. M. (1941) *Trans. Ophthal. Soc. Aust.* 3, 35.
Grueneberg, H. (1947) Animal Genetics and Medicine. London; p. 112.
Harman, N. B. (1909) *Trans. ophthal. Soc. U.K.* 29, 296.
Knapp, F. N. (1926) *Amer. J. Ophthal.* 9, 683.
Lowe, R. F. (1949) *Brit. J. Ophthal.* 33, 131.
Macklin, M. T. (1927) *Canad. med. Ass. J.* 17, 940.
Manson, J. S. (1928) Observations on Human Heredity. London; p. 4.
Penrose, L. S. (1949) Biology of Mental Defect. London; p. 94.
Saebø, J. (1949) *Brit. J. Ophthal.* 33, 601.
Wilson, S. A. K. (1940) Neurology. London; p. 104.
Worth, C. (1930) May and Worth's Diseases of the Eye. London; p. 239.

ORNITHOSIS

ISOLATION OF THE VIRUS FROM A CAS

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THE virus of ornithosis, a member of the psitta lymphogranuloma-venereum group, closely resen that of psittacosis but can be distinguished by differe in its infectivity for animals. Psittacosis is a disea psittacine birds (parrots and budgerigars) whic communicable to man. The term ornithosis is use similar infections occurring among a wide rang non-psittacine birds, including fulmars, domestic f pigeons, and ducks. The ecology of psittacosis ornithosis has been fully reviewed by Meyer (1942).

The virus of psittacosis has been isolated from hu cases of respiratory infection (Bedson et al. 1930, T et al. 1939), but isolation of the virus of ornithosis not yet been reported in this country. Recovery o ornithosis virus from the throat-washings of a po dealer with atypical pneumonia and serological evid of recent infection with this virus is therefore desc here.

CASE-RECORD

A male poultry dealer, aged 42, was admitted to Manchester Royal Infirmary on Nov. 7, 1950, under the of Dr. C. S. D. Don, with frontal headache, cough, and across the back of the lower chest. His illness had st suddenly four days previously with shivering and swea He had been treated by his doctor with a sulphonamid three days without effect.

On admission he looked ill and was perspiring freely was mentally alert. His temperature was 100·6°F, pulse-rate 95 and respirations 28 per min. Numerous c crepitations were audible over the right, and to a lesser de the left, lower lobes. No other abnormality was discov on physical examination. A radiograph of the chest normal.

Treatment and Progress.—Next day his condition unchanged. As he complained of persistent headache, cerebrospinal fluid was examined and found to be nor Specimens of blood and throat washings were sent for v isolation, and treatment with penicillin 200,000 units hourly was started. Two days after admission he apyrexial and feeling much better. Penicillin was disconti eight days after admission, and the remainder of his in hospital was without incident. He returned hom Nov. 20, 1950. A further chest radiograph on that was normal.

Other investigations.—On Nov. 7, 1950, a blood-count sh red cells 5,300,000 per c.mm., Hb 15·4 g. per 100 ml., cells 7700 per c.mm. (polymorphs 78%, lymphocytes 1 Cold agglutinin and Paul-Bunnell tests were both neg on Nov. 8. Normal upper-respiratory-tract organisms grown from the sputum on Nov. 9, and no tubercle b were seen on microscopy. A Frei test done on Nov. 27 negative.

VIRUS STUDIES

As the patient lived near an area in which lymphoc choriomeningitis is endemic (Duncan et al. 1951), virus of this disease was considered to be a pos cause of his atypical pneumonia.

5 ml. of throat washings and 2 ml. of blood were injected intraperitoneally into two pairs of guineapigs. A five days one animal from each pair was pyrexial. T two were killed, and a 1 in 20 emulsion of their spleens injected intracerebrally into two batches of mice.

All the mice inoculated with the emulsion from the guinea-g which had been injected with blood died of *Salmonella phimurium* infection. The other batch became ill with ffled fur, tremors, and slight conjunctival exudate, and were oribund by the fifth day. Smears from the brains of these ice contained numerous pus cells but no organisms; aerobic d anaerobic cultures were sterile.

Intracerebral passage of brain from these animals produced e same clinical features in a second batch of mice. Smears om the brains of these mice showed numerous pus cells and ementary bodies morphologically identical with those of ittacosis. A 1 in 10 suspension of brain from these mice was fective when diluted 10^{-4} and injected intracerebrally into her mice. Intraperitoneal injection of 0·5 ml. of the spension was either without visible effect, or the mice veloped ascites from which they recovered. After ten days virus could be isolated from their spleens.

These findings indicated that the infective agent was e virus of ornithosis rather than that of psittacosis. hich is pathogenic to mice by both the intracerebral d intraperitoneal routes (Meyer et al. 1942).

In the complement-fixation test allantoic fluid con-taining the virus isolated from the patient was used as tigen because the virus grew well in the allantoic vity of the developing chick embryo. The results of is test were:

Days from onset of illness	*Complement-fixation titre* (Highest serum dilution giving more than 50% fixation)
5	<1 in 5
11	1 in 40
18	1 in 80
36	1 in 40
70	1 in 20

Professor Bedson kindly confirmed the presence of lementary bodies of the psittacosis group in the mouse-rain smears. He also found that the serum obtained n the eleventh day fixed complement with psittacosis ntigen. Fixation was complete at a dilution of 1 in 16 nd almost complete at 1 in 32. Complement-fixation ests with the serum of two members of the atient's family and of the assistant in his shop were egative.

The source of this patient's infection was not determined. However, the virus of ornithosis was isolated rom one of six pigeons trapped in the Manchester area.

DISCUSSION

Ornithosis was diagnosed in this case for the following reasons: (1) the virus was pathogenic to mice by the intracerebral route only, while that of psittacosis is also pathogenic by the intraperitoneal route; (2) mouse-adapted virus grew well in the allantoic cavity of the developing chick embryo without the preliminary yolk-sac passage required for the virus of psittacosis: and (3) the patient handled large numbers of pigeons, fowls, ducks, and turkeys in his poultry shop.

Although a budgerigar was kept in his home it had not been sick; nor had any member of the patient's family had an illness suggestive of atypical pneumonia.

No conclusion can be drawn about the effect of penicillin on the course of this patient's illness; for the treatment began only twelve hours before the tempera-ture fell and clinical improvement started. Wolins (1948) reported a satisfactory response to treatment with penicillin 400,000 units daily in 4 of 6 patients with ornithosis; the same dose of penicillin was without effect in the remaining 2. Tasker (1949) has recorded a case of psittacosis in which there was a dramatic response to treatment with penicillin 2,000,000 units daily.

SUMMARY

Ornithosis infection in a poulterer is described.

The methods used for isolation and identification of the virus are recorded.

The serological evidence of infection is given.

Our thanks are due to Dr. C. S. D. Don for permission to publish details of the patient; to Prof. S. P. Bedson, F.R.S., for help in confirming the diagnosis; to Mr. J. Norris, superintendent of Manchester Town Hall, for his department's help in obtaining pigeons for examination; and to Prof. H. B. Maitland for helpful criticism and advice.

REFERENCES

Bedson, S. P., Western, G. T., Simpson, S. L. (1930) *Lancet*, i, 235.
Duncan, P. R., Thomas, A. E., Tobin, J. O'H. (1951) *Ibid*, i, 956.
Meyer, K. F. (1942) *Medicine, Baltimore*, 21, 175.
— Eddie, B., Yanamura, H. Y. (1942) *Proc. Soc. exp. Biol., N.Y.* 49, 609.
Tasker, J. R. (1949) *Brit. med. J.* ii, 362.
Troup, A. G., Adam, R., Bedson, S. P. (1939) *Ibid*, i, 51.
Wolins, W. (1948) *Amer. J. med. Sci.* 216, 551.

THE ESTIMATION OF FORMALDEHYDOGENIC STEROIDS

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IN the method used by Hollander et al. (1951) for estimating formaldehydogenic steroids the formaldehyde is determined by isothermal distillation directly into the chromotropic acid reagent using a Conway micro-diffusion unit. After distillation is complete, the chromotropic acid-formaldehyde mixture is transferred to a test-tube cuvette and heated at 100°C for 30 minutes, and the colour is measured at 570 mμ in the usual way.

This method would be easier if the colour development could be carried out in the Conway unit. This can be done by allowing the distillation to take place at 50°C. We have found the following procedure to be the most satisfactory.

1 ml. of formaldehyde-containing solution (0·4–4 μg. per ml., preferably in 5% acetic acid) is pipetted into the inner chamber of a standard Conway unit (Gallenkamp no. 1), the outer chamber of which contains 2 ml. of 0·2% chromotropic acid in 15*M* sulphuric acid. The unit is sealed and placed in an oven at 50°C overnight (17 hours). Appropriate blanks are also set up. Next morning the extinctions are measured at 570 mμ ('Unicam D.G.' spectrophotometer, 1 cm. cells).

Under these conditions recovery of formaldehyde is quantitative (>95%), the colours formed being equal to those obtained by heating mixtures of 1 ml. of formaldehyde solution and 2 ml. of chromotropic reagent at 100°C for 30 minutes. 1·5 μg. of HCHO gives an extinction of about 0·26, the relationship between extinction and concentration being linear over the range cited above. The specific colour is very stable, and after reaching its maximum it appears to be unaffected by further heating for several hours. The recovery of formaldehyde from periodate-oxidised solutions of cortisone is also quantitative. The equivalent of 5–50 μg. of cortisone can be estimated satisfactorily, 25 μg. giving an extinction of 0·35. Other steroids are being studied.

This method has been used for the estimation of formaldehydogenic steroids (F.S.) in urinary extracts prepared after hydrolysis of the steroid conjugates with β-glucuronidase. The F.S. excretion of several rheumatoid arthritic women, aged 40–50, was found to be 6·5–13·0 mg. per 24 hours, these results being some 10–20 times greater than those obtained after hydrolysis at pH1 for 18 hours, as in older methods. In preliminary experiments, a considerable increase in F.S. excretion was noted after administration of A.C.T.H. by intramuscular or intravenous infusion during 8 hours. Thus, in two patients who received 20 I.U. intravenously, the urinary F.S. excretion increased from control values of 10·1 and 9·4 mg. per 24 hours to 24·8 and 23·6 mg. per 24 hours respectively on the day of the infusion. Intramuscular infusions of A.C.T.H. 75–100 I.U. have usually led to increased F.S. excretion amounting to 60–100% of the control values; in one case 150 I.U. intramuscularly increased the urinary F.S. from 6·7 to 37 mg. per 24 hours. In most cases the F.S. excretion decreased to control values, or slightly lower, on the day following the infusion. Similar but smaller changes were observed in the urinary 17-ketosteroids.

It has also been noted that during treatment with cortisone the excretion of β-glucuronidase-liberated formaldehydogenic steroids increases by an amount equivalent to 15–25% of the administered cortisone.

We wish to thank Dr. W. S. C. Copeman and his colleagues for enabling us to make these studies on their patients. Thanks are also due to Dr. A. E. Kellie for helpful advice during part of the work, and to Dr. E. C. Kendall for a gift of cortisone.

REFERENCE

Hollander, V. P., DiMauro, S., Pearson, O. H. (1951) *Endocrinology*, 49, 617.

A PITUITARY TUBERCULOMA

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PITUITARY tuberculoma, as an *isolated* intracranial lesion, is extremely rare.

Coleman and Meredith (1940), before publishing such a case, circularised the neurosurgeons and neuropathologists of the United States and found that none of them had seen a tuberculoma confined to the pituitary fossa.

Anderson (1928), in his review of tuberculomas of the central nervous system, included no tuberculomas of the pituitary gland.

Riecker and Curtis (1932), in their account of the necropsies of 24 cases of Simmonds' disease, found the destructive lesion to be tuberculous in 2 instances.

Kirshbaum and Levy (1941) described 2 cases of pituitary tuberculoma with well-marked signs of anterior-pituitary insufficiency. Histologically the lesions were typical of tuberculosis, but no tubercle bacilli were detected.

Coleman and Meredith's case is the only one published in which the tuberculoma behaved as an expanding lesion, causing headache, optic atrophy, bitemporal hemianopia, and enlargement of the sella turcica. Operation relieved the headache and visual disturbances, and the patient was perfectly well when seen three and a half years later. The microscopical appearance was typical of chronic tuberculosis, but no tubercle bacilli were found.

The patient whose case is described below gave no apparent clinical evidence of pituitary deficiency, though no normal parenchyma was seen in the sections subsequently examined.

CASE-RECORD

A man, aged 52, was admitted to hospital on Aug. 14, 1948, with a history of violent *frontal and retro-orbital headaches*, which had come on intermittently for four and a half months and were usually associated with vomiting. There were no other symptoms, and there was no history of *accident or previous illness*. The family history was irrelevant.

Examination.—He was a well-built intelligent man with intermittent pyrexia which did not exceed 100°F. His pulse-rate was normal. His left optic disc appeared a *little* paler than the right. Visual acuity was 6/6 on the right, and 6/18 on the left. The Bjerrum screen was not available, but examined with the perimeter the right field appeared to show an early bundle defect below, and the left field both upper and lower bundle defects. A complete examination of all other systems was negative, except that the blood-p was 140/100 mm. Hg.

The alternative diagnoses were sphenoidal sinusitis and lesion of the pituitary gland.

Investigations.—Radiography of the skull showed faction of the posterior clinoid processes and dorsum se but their outlines were just visible; there was no enlargeme of the pituitary fossa. Several films of this region reveal diminished translucency of the sphenoidal sinus. Radi graphs of the lungs were normal. Lumbar puncture produc cerebrospinal fluid (C.S.F.) under a pressure of 90 mm., co taining 27 lymphocytes per c.mm., 90 mg. of protein per 1 ml., and 720 mg. of chloride per 100 ml.; there were tubercle bacilli, and culture was negative. Blood examinati showed Hb 80%, red cells 3,900,000 per c.mm., white ce 9400 per c.mm. (polymorphs 67%, lymphocytes 28%, mor cytes 5%). The erythrocyte-sedimentation rate (Westergre was 51 mm. in an hour. Wassermann and Kahn reactions we negative.

Air encephalography on Aug. 24, 1948, revealed abnormality of the ventricles or of those sulci which we filled with air; but air which collected over the pituita fossa suggested slight upward bulging of the sell diaphragm.

Treatment and Progress.—In view of the pleocytosis in t C.S.F. and the intermittent pyrexia, tuberculous meningi was diagnosed, and a course of intramuscular and intrathe streptomycin was begun. No further developments occurre and no new information was obtained after repeated examin tion of the patient, except that the blood, investigated duri apyrexial periods, showed a relative lymphocytosis; Feb. 9, 1949, the white-cell count was 8200 per c.mm (polymorphs 42%, lymphocytes 57%, monocytes 1%).

When reviewed on Feb. 14, 1949, the patient still complain of frontal and retro-orbital headache, with episodes of naus and vomiting, and his temperature was 99°F. The conclusi was reached that there was a chronic inflammatory lesion or around the pituitary fossa with some degree of meninge reaction. The tubercle bacillus remained the suspecte organism, but it could not be demonstrated in the C.S. either directly or by guineapig inoculation.

On March 16, 1949, the patient left the neurosurgic department to continue streptomycin treatment elsewher On March 25, 1949, he was given two injections of 10 units insulin to stimulate his appetite, which had become very poo The first injection was given at 6 A.M. and the second 7.30 P.M. At 9 P.M. he was found to be in coma; he wa sweating profusely, and his pulse was almost imperceptibl He was given an injection of 10 minims of adrenaline but h died at 9.35 P.M. while an intravenous injection of glucos was being prepared.

At necropsy (Dr. I. L. M. Larkin) on March 29, 1949, small area of consolidation, with a central patch of destructio was found at the apex of the left lung. The pituitary glan seemed to bulge slightly upwards, though the optic nerves an chiasm were not compressed. The gland was represented by tough capsule surrounding a caseous interior. The floor the pituitary fossa had been eroded, and the posterior clinoi processes and the dorsum sellæ were very thin. The interi of the sphenoidal sinus was completely filled with œdema tous mucosa. No abnormality was discovered in a other organ.

Histology.—Dr. E. A. Atkinson reported on sections o pituitary gland and lung as follows: "Remains of pituitar tissue occupy the centre of the mass, which also include spicules of bone. The mass consists largely of dense fibrou tissue enclosing giant-cell systems with epithelioid cell confluent areas of caseation, lymphocytes, and plasma cell The histological picture is consistent with tuberculosi Tubercle bacilli were not demonstrated, but in view of th chronic nature of the inflammatory reaction this is not sur prising. The inflammatory process has resulted in the almos complete destruction of both anterior and posterior lobes together with the floor of the pituitary fossa. The sectio of lung shows extensive subacute caseating tuberculosis onl thinly walled off by fibrous tissue. Acid-fast bacilli wer demonstrated by fluorescence microscopy."

COMMENTS

Pituitary tuberculoma may cause persistent fronta headache associated with anterior-pituitary insufficienc ich may, or may not, be evident clinically. Only one stance is recorded in which the tuberculoma behaved *an expanding* lesion, causing optic atrophy, bitemporal mianopia, and enlargement of the sella turcica.

My patient showed minimal interference with the sual pathways and no apparent endocrine disorder, ough the fatal reaction to a small dose of insulin ggested a severe anterior-pituitary insufficiency.

Patients with Simmonds' disease are sensitive to sulin; with a given dose the blood-sugar level is wered more than in a healthy person, and it takes nger to return to normal. The insulin-tolerance test r Simmonds' disease is based on this observation raser and Smith 1941).

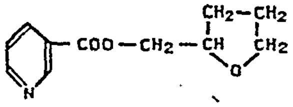
REFERENCES

iderson, F. N. (1928) *Arch. Neurol. Psychiat.* 20, 354.
leman, C. C., Meredith, J. M. (1940) *Ibid.* 44, 1076.
aser, R., Smith, P. H. (1941) *Quart. J. Med.* 10, 297.
rshbaum, J. D., Lovy, H. A. (1941) *Arch. intern. Med* 68, 1095.
ecker, H. H., Curtis, A. C. (1932) *J. Amer. med. Ass.* 99, 110.

Preliminary Communication

KIN RESPONSE TO LOCAL APPLICATION OF NICOTINIC ACID ESTER IN RHEUMATOID ARTHRITIS

'Trafuril' is a cream containing 5% by weight of tra-hydro-furfuryl nicotinic acid ester in a water-iscible base. The structural formula of the active gent is:



ts local application is said to be beneficial in rheumatic onditions.

The preparation was first tested on normal controls. quarter of an inch of cream squeezed from the tube ras applied to the flexor surface of the forearm and ubbed in until it disappeared. A variable time after pplication, but as a rule within 5–10 minutes, hyperemia was evident at the site of application, usually ccompanied by a sensation of tingling and heat. In ome cases there was also slight œdema, usually at the dge of the area of erythema. The effect lasted from /2 to 1 hour and then gradually faded. In some subjects mild erythema occurred at first and the full response ppeared in 2–4 hours.

The response was more prompt when the skin was warm, and it was apt to be delayed and less intense when the skin was cold. The response was greater in those with fair skin and less intense in the older people. These findings are in agreement with those of Stark-Mittelholzer[1] and Strehler.[2] In two subjects a patch of erythema appeared on an untreated area—the opposite forearm and the face. This phenomenon has also been noted by Strehler.

The cream was next tried in patients with rheumatoid arthritis. In those with obvious active disease and constitutional disturbance, there was no response over the affected joints, forearm, or front of the chest. In those with less acute manifestations a mild erythema only was produced, often without the sensation of heat and tingling. In cases with minimal evidence of activity or those in remission a normal or subnormal response was the rule. It was therefore decided to study the effects of A.C.T.H. or cortisone on the skin reactions in those patients with active disease who were non-reactors.

A woman with active disease affecting many joints was given 50 mg. of cortisone acetate by mouth daily. Her condition was only slightly improved and the skin response remained negative. She was admitted to hospital and given 25 mg. of A.C.T.H. every 6 hours by subcutaneous injection. Her symptomatic response was prompt and the skin test on the 4th day produced an intense spreading flare at the site of application, and a sensation of tingling and burning.

A second woman who was a non-reactor was given 100 mg. of cortisone acetate by mouth daily. This brought rapid symptomatic relief, and her skin response was normal at the end of a week.

Two further women who were non-reactors were given 12·5 mg. of A.C.T.H. subcutaneously every 6 hours, but relief was only slight; the skin response remained negative and did not become normal until the dosage was raised to 20 mg. 6-hourly.

A man of 40, who had had acute rheumatic fever at the age of 10, was admitted with a history of fever, with acute pain and stiffness in all joints; there were signs of carditis with a pericardial friction rub. His skin response over the affected joints and forearm was negative. He was given 25 mg. of A.C.T.H. subcutaneously every 6 hours. His temperature fell from 103°F to normal within 24 hours. All pain and stiffness disappeared, but the pericardial rub was still present after 2 days, when a second skin test was again negative. On the 6th day his condition was good and the pericardial rub had disappeared; a prompt and intense skin response developed within 10 minutes.

The skin reaction has also been tested in a few cases of osteo-arthritis, with normal results. In three cases of tuberculous arthritis the response has also been normal.

The exact mode of action of nicotinic acid and its derivatives is not known; it is presumed to have a transient action directly on the capillaries and skin arterioles. Strehler suggests that a histamine-like substance is released, though he found that the hyperæmia could not be inhibited by local or internal administration of anti-histamine drugs. Stark-Mittelholzer found that pricking the skin with trafuril produced no response, in contrast to histamine, and therefore presumed its action to be directly on the capillaries and small arterioles. It is unlikely that the reaction is one of histamine release, for it is enhanced by both A.C.T.H. and cortisone.

The reaction is obviously one of fundamental importance and worthy of further study. It may prove valuable in the elucidation of the action of A.C.T.H. and cortisone, and also of the abnormal peripheral circulation in rheumatoid arthritis and allied conditions. The reaction may also be of value in differential diagnosis, and in the assessment of activity and response to treatment.

There are indications that there is an increased tolerance to nicotinic acid by mouth in these patients and it is permissible to predict that the intravenous response will also be abnormal. These investigations are being continued.

Our thanks are due to Messrs. Ciba Ltd. for the supplies of trafuril.

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[1] Stark-Mittelholzer, O. *Dermatologica*, 1950, 100, 23.
[2] Strehler, E. *Schweiz. med. Wschr.* 1949, 79, 144.

"... Mr. Butler ... has decided how the financial load of his Budget shall be divided up between families. But he cannot determine how the load shall be shared within them .... In fact earnings are usually divided into two portions, one spent by the husband and the other spent by the wife. Out of his portion the husband may buy most of the cigarettes; and out of hers, the wife may buy most of the food .... If wives' allowances do not rise they will have to bear the full burden of the rise in food prices out of their own portion of the family income."—MICHAEL YOUNG, *The New Statesman*, March 29, 1952, p. 365.

Reviews of Books

The Rh Blood Groups and their Clinical Effects

P. L. MOLLISON, A. E. MOURANT, and R. R. RACE. Medical Research Council Memorandum no. 27. London: H.M. Stationery Office. 1952. Pp. 72. 3*s*.

THIS is a revised version of the excellent and valuable memorandum no. 19, published in 1948. A few references have been added and a few paragraphs expanded, mostly in the section on Rh testing; the use of papain instead of trypsin in Rh testing is fully noted; the use of dextran is not approved; more details are given about the preparation of anti-human-globulin serum. The tables are now published with arabic instead of roman numerals; the word "anthropology" has been substituted for "ethnology." It is disappointing to find that the opportunity has not been taken to clear up the nomenclature difficulties. To anyone unfamiliar with A. S. Wiener's nomenclature, the "short symbols" in table 5 must appear arbitrary and unnecessarily confusing; why should cDe be represented by R_0, CDe by R_1, Cde by R', and CDE by R_z? The authors remain convinced that Fisher's notation is the only one capable of fully designating the genes and genotypes; so, if short symbols are needed, it would be preferable to relate them in a clearly recognisable manner to the CDE/cde system. Nevertheless this memorandum, like its predecessor, remains the best short practical account of the subject.

Leprosy

An addendum to the third edition of "Leprosy." Sir LEONARD ROGERS, K.C.S.I., C.I.E., M.D., F.R.C.S., F.R.C.P.; ERNEST MUIR, C.M.G., C.I.E., M.D., F.R.C.S.E. Bristol: John Wright & Sons. 1951. Pp. 16. 2*s*. 6*d*.

THIS addendum brings the 1945 edition of the textbook on leprosy by these authors up to date. In that volume only a short reference was made to 'Promin' and 'Diasone,' the first two sulphones used in the treatment of leprosy. Now a short history of diaminodiphenylsulphone (D.D.S.), the parent substance, and its derivatives, promin, diasone, and 'Sulphetrone' is given; and two others, 'Promizole' and 'Promacetin,' are mentioned. The toxic effects of D.D.S., formerly dreaded, have proved to be chiefly due to excessive dosage. The chemical formulæ, the action, the dosage and the best methods of administration, and the toxic effects of the sulphones, are described, and complications such as dermatitis and glandular fever discussed. The difference between the ordinary lepra reaction and that due to the sulphones is pointed out, and the fact that the latter may accelerate the elimination of the lepra bacilli from the body is noted. The authors advise on the choice of the most suitable sulphone and the means of controlling progress under treatment and describe a method of estimating the increase or decrease of the number of bacilli in the body. Notes on other preparations used in treatment, notably streptomycin, thiosemicarbazone, and cepharanthin, are included.

This addendum emphasises the great change that has taken place in these last few years in the outlook for patients with Hansen's disease, and the need for teaching the public that leprosy is not dangerously infective, and should carry no stigma.

Steroids in Experimental and Clinical Practice

Editor: ABRAHAM WHITE. *Philadelphia: Blakiston* Co. London: J. & A. Churchill. 1951. Pp. 415. 50*s*.

THIS book is the record of a conference held in Mexico in January, 1951, under the auspices of Syntex-Chemical Specialities Inc., to discuss the experimental and clinical actions of the 11-desoxysteroids, especially Δ^5 pregnenolone. These compounds, produced by Syntex from Mexican plant sapogenins, had been supplied by the company to the investigators whose results were reported. The communications covered (1) general studies on steroid metabolism, (2) the use of pregnenolone in the treatment of rheumatoid arthritis, and (3) certain specific actions of steroids on human and animal tissues.

The general studies, and the discussions arising out of them, were of high standard, and are of great interest though much of the work has already been published. Selye reviewed the actions of the desoxysteroids, and p forward his controversial views on the "mineralo-corticoi mimetic" actions of somatotropic hormone and its relati to stress. Zaffaroni described the identification of 17-hydrox corticosterone and of corticosterone in adrenal venous bloo and proposed as an explanation for the reputed benefic action of pregnenolone on rheumatoid arthritis the t *formation of the drug by the adrenal gland to* 17-hydrox corticosterone—a change demonstrable by perfusion expe ments. The editor discussed thoughtfully problems of resear into steroid therapy and steroid metabolism. Pincus and co-workers reported metabolic and excretion studies adrenal function during cortisone and pregnenolone therap they found oral cortisone less toxic than parenteral cortiso Dobriner spoke of the urinary steroid excretion patte occurring in health, after hormone treatment, and in diseas attention was drawn to the problem of the excretion of hydroxyætiocholanolone in cancer and in Cushing's disea

The clinical papers varied in quality; and only th series of cases of rheumatoid arthritis where there b been no proper control of pregnenolone therapy by t use of placebos, or by objective measurement of amelio tion, showed any "significant" improvement.

Three observers—Conn, Sprague, and Danowski—w invited to summarise and comment on these reports: t agreed that pregnenolone and allied compounds had not b shown to have any definite clinical or metabolic action man, and that available resources should be concentrated the study of compounds of known activity. Other commu cations described the partially beneficial results of treatm by progesterone of seminal inadequacy and of carcinoma the cervix, and by androgen derivatives of advanced carcino of the breast: a review of the general use of steroids treatment of cancer was also presented.

Papers of a more specialised nature described effects of pregnenolone on cardiac muscle in dogs, steroids on growth of chick embryos and of mo lymphosarcomata, and of 3-ketosteroids on œstrog induced fibromata in guineapigs.

Die Erbpathologie der sogenannten angeborenen Hü verrenkung.

Prof. Dr. med. KARLHEINZ IDELBERGER, direc of the orthopædic department of the surgical cli of the University of Göttingen. Munich: Urban Schwarzenberg. 1951. Pp. 80. D.M. 11.

THIS careful study of congenital dislocation of t hip is based on an unselected series of 138 twin pa with at least one affected partner. These were extract from 22,004 cases treated between 1921 and 1939 numerous orthopædic hospitals covering most of Germa and Austria, and the survey ultimately included those primary cases who were members of a twin p and whose other partner was still alive at the time of t study. All these, together with their near relatives, w personally examined by Professor Idelberger, who a used hospital records, X-ray films, and other materi Of 29 pairs of monozygotic twins, both had frank d locations in 10 instances, and in 2 further instances second twin had a dysplasia of the acetabulum. contrast, among 52 dizygotic pairs of like sex no ca were seen in which both twins were affected; and th were only 3 cases among 57 dizygotic pairs of unlike s Here is evidence that genetic factors are partly responsi for this anomaly. The data presented in this book of no evidence that external mechanical factors have a important rôle in the causation of dislocation of the h On the other hand, the fact that in something like tw thirds of the identical twins only one was affected sho that the genetic tendency is influenced by other facto The most important of these is sex, females being affect more than five times as often as males. Otherwi specific environmental factors (e.g., the twin pregnan as such, maternal age or parity, or birth trauma) see to have little effect. Apparently most of the non-gene variation is due to accidents of development which far defy a more detailed analysis. It should be m tioned that in Professor Idelberger's series dysplasia the acetabulum was rare among the relatives of th affected; Faber, whose patients came mainly fr Saxony where dislocation is particularly common, fou the opposite.

THE LANCET

LONDON: SATURDAY, APRIL 5, 1952

"Politics"

In the past week or two the National Health Service has been in the political foreground. A few days after the publication of the Estimates of next year's expenditure[1] came the Danckwerts award on the remuneration of general practitioners,[2] followed by major debates in both Houses of Parliament. The Lords considered the working of the service in general, and the Commons took the second reading of the latest National Health Service Bill, which imposes new charges for dental treatment and renews the proposal to collect money from patients for each prescription issued.

In his important speech in the Upper House Lord MORAN said: "When you are told that these charges on prescriptions and for dental treatment have demolished the structure of this health service, that is politics. No doctor would believe that criticism. Surely the foundations of this service are not quite as shaky as that." Looked at non-politically, the situation seems plain enough. If, as successive Chancellors have insisted, the N.H.S. is not to cost the taxpayer more than £400 million, and if prices continue to rise, and if we are to use the expensive new techniques and remedies that science is perpetually devising, it is obvious that the service will either have to reduce its expenditure at certain points, or charge the public for some of its benefits, or do both these things. What is in fact being done is to reduce capital expenditure on hospitals and at the same time ask the public to contribute as patients an additional £20 million a year which they cannot conveniently find as taxpayers. As Lord MORAN remarked, "if you say to the people 'Here is a free service' and then you put a charge here and a charge there, it is apt to be politically inconvenient"; but doctors, as doctors, are concerned with such alterations only in so far as they affect the character of the service. How the N.H.S. is financed is a matter for Parliament, which also has a right to decide, with the Health Ministers' guidance, whether it is better to offer, let us say, free dentures or a free bed in hospital. On the other hand the profession would be very closely concerned if it were found, for example, that the charge for prescriptions, or any other financial device, had the effect of preventing sick people from seeing their doctor or getting treatment when they ought to do so; and though we should welcome a lessening of demands on practitioners, and of unnecessary medicine-drinking, the Commons debate left us feeling that the objections to this particular charge have not yet been overcome, and that it is not going to prove acceptable as a permanent feature of the service. Mr. IAIN MACLEOD pointed out that, particularly with poorer people, "health expenditure is a marginal expenditure and one of the first things which goes by the board if anything has to be paid for."

Lord WEBB-JOHNSON said that, though it would be wrong to uproot the N.H.S. only three years after planting, its growth would probably benefit by some radical pruning. Likewise Mr. CROOKSHANK indicated that the object of his Bill was not merely to reduce expenditure: he wants to strengthen the plant by pruning or rearranging some of the present services —"indeed by getting the emphasis altered in the right direction." All agree at least that the £50 million spent annually on drugs includes much waste, and Mr. CROOKSHANK hopes to reduce this by the prescription charge. Dentists in the N.H.S. are spending too much of their limited time on adults and too little on children, and by making adults pay the first £1 required for treatment the Minister hopes to promote more dental care for the young. We shall all be glad if these things are achieved. But, if the object is really to alter the emphasis of the service in the right direction, what are we to say of Estimates that give the hospitals an even larger proportion of its resources than they had before? For years it has been evident that the N.H.S. has got gravely out of balance by steadily preferring the needs of the patient in hospital to the needs of the patient out of hospital; and, though the Ministry of Health has seemed to recognise the danger, the unbalancing process has continued just the same. It is an ironical commentary on the strategic planning of the service that the first big step towards restoring equilibrium has been taken by a High Court judge who was concerned with a problem of social economics and not in the least with the improvement of medical care. As Mr. MACLEOD said, the Danckwerts award, by breaking the irrational ceiling of £400 million, has given us an opportunity to reconsider the proportion of our national income that ought to be spent on health and also to reconsider expenditure on the different parts of the service. "We have had a situation in the health service," he said, "in which we paid more in gross income to 10,000 dentists than to 20,000 general practitioners. We had a situation—and indeed it is the situation at this moment before this Bill passes—in which the expenditure on drugs in this country is £11 million more than the amount paid to the general practitioner."

We may be thankful that the outlook for general practice has now considerably improved, but we cannot be satisfied that such improvement should be almost accidental. The smaller the means at the disposal of the N.H.S. the more important is true economy of effort—that is to say expenditure on what is most desirable. We all share the Minister's aims; but both pruning and fertilising are a tricky business, and the development of so immense an undertaking as the health service needs to be not only wise but consistent over the years. That is why the casual or political decision may be so dangerous; and we venture to repeat what we said at the beginning of last year: "if a sense of confidence and purpose and hope is to be created" in those who work the service "they must feel that it has a development policy, and that its decisions are based on that policy and on equity—not on hard bargaining, and certainly not on party politics."

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[1] See *Lancet*, March 29, 1952, p. 661.

[2] *Ibid*, pp. 652, 662.

Isonicotinic Acid Hydrazide

AFTER the preliminary symposium by the Sea View Hospital[1] on the hydrazine derivatives of isonicotinic acid, found to be active in tuberculosis, comes now a collection of important investigations reported in the April issue of the *American Review of Tuberculosis*.

Studies on the pharmacology of these drugs have been made at New York Hospital by ELMENDORF et al.,[2] who since November, 1951, have administered isonicotinic acid hydrazide to adult patients with moderately or far advanced tuberculosis. With a few exceptions, the patients had had long courses of streptomycin and P.A.S., and were discharging tubercle bacilli which were streptomycin-resistant in vitro. The drug was given orally, at twelve-hour intervals, in daily doses of 3 mg. per kg. body-weight. After a single oral dose of 3 mg. per kg. the drug was absorbed promptly; maximum concentrations (1·3–3·4 μg. per ml.) were attained in the plasma between one and six hours after injection. Among patients who had been receiving 1·5 mg. per kg. twice daily for at least a week, there were concentrations of 0·60 to 1·48 μg. per ml. in the plasma three hours after administration (a concentration of 0·06 μg. per ml. completely inhibits the H37Rv strain of *Mycobacterium tuberculosis* for fourteen days in vitro). There was no evidence that with long-continued administration the drug was accumulated. Transfer of the drug into the cerebrospinal fluid (C.S.F.) after oral administration was studied in 9 patients, of whom 5 had active tuberculous meningitis. Appreciable concentrations of the drug were found in the C.S.F. within three hours of an oral dose; in the cases of meningitis the level was 1·8–4·1 μg. per ml. Aliquots of C.S.F. and plasma were assayed biologically (against H37Rv) and chemically. The results show reasonable correlation between the two methods of assay, and demonstrate that the drug is distributed in plasma and C.S.F. in an active state.

Results of toxicity experiments in animals are described in two papers.[3] [4] Single doses in the acutely toxic range induce signs of central nervous system stimulation terminating in death from respiratory failure. Mice receiving toxic doses develop clonic convulsions, running movements, and prostration, which terminate in tonic limb extension and death within twenty-four hours. In rats and rabbits the parent substance is less toxic than the isopropyl derivative. In dogs, with doses of 50–100 mg. per kg., salivation and vomiting occur after half an hour, followed by anxiety and convulsions which become continuous and terminate in death. The toxic results were similar whether the drug was given intravenously or orally. Subacute toxicity in rats is evidenced by anorexia, loss of body-weight, occasional convulsions, and slight hepatic damage. In dogs to which the drug was given at 25 mg. per kg., at the end of five days the oxyhæmoglobin, as well as the total hæmoglobin, of the blood was significantly reduced. When administered repeatedly to two dogs in a dose of 28 mg. per kg. the isopropyl derivative induced evident anæmia after five intravenous injections. In one series of long-term toxicity studies in dogs,[3] the hydrazide was administered intravenously to each of three dogs at dose levels of 1, 5, and 20 mg. per kg., five days per week for thirteen weeks. While the dog on 1 mg. per kg. exhibited no signs of toxicity, the dog on 5 mg. per kg. occasionally exhibited anorexia. The animal on 20 mg. per kg. in addition had occasional emesis, failed to gain weight, and often appeared lethargic. In chronic toxicity tests of the isopropyl derivative necropsy of the dogs revealed gross pathological changes, which were most manifest in the spleen, bone-marrow, liver, and kidney. In another series chronic administration to dogs of 10–25 mg. per kg. resulted in anorexia, loss of body-weight, ataxia, tonic and clonic convulsions, fatty degeneration of the liver, and jaundice.

ROBITZEK and SELIKOFF[5] report in some detail the toxic effects in man. Various doses were used, ranging from 1 to 10 mg. per kg.; while the therapeutic effect appeared to be proportionately greater with increasing doses, so also were the side-effects. Early observation indicated central nervous stimulation. Of 44 cases twitching of the extremities was observed in 37, increased deep reflexes in 26, bladder-sphincter hypertonia in 13, and insomnia in 17. Constipation and dizziness were also common. Symptoms appeared most commonly in the second to fourth weeks of treatment, and were more usual with the isopropyl derivative than with the parent substance. ELMENDORF et al.[2] administered the drug daily for periods of four to sixteen weeks without evidence of serious toxic reaction, at doses of 3 mg. per kg.; and the discrepancy between their findings and those reported above is unexplained. They state, however, that "it is probable that instances of toxicity similar to those seen in dogs will be observed when the drug is administered at more frequent intervals, in a larger daily dose, or for a longer period of time." They emphasise that in man large doses are inadvisable except in very special circumstances and with very close observation.

BERNSTEIN et al.[6] report on studies of the drug's activity against tuberculosis in the mouse. In mice infected with the bovine strain, isonicotinic acid hydrazide, administered in doses of 7–25 mg. per kg., produced a significant increase in survival-time. At these doses all mice survived; with a dose of 3 mg. per kg. only one of ten survived; and at 2 mg. per kg. all died. When treatment was delayed for seven days after infection, on doses of 9–16 mg. per kg. all mice survived. When treatment was delayed for fourteen days, most of the mice were moribund; despite this advanced stage of disease, subcutaneous administration brought about complete recovery in a high percentage. STEENKEN and WOLINSKY[7] found that guineapigs infected subcutaneously with human tubercle bacilli, and treated three weeks later with isopropyl derivative, showed little evidence of tuberculosis when killed seventy-three days after infection, and guineapigs infected intracerebrally remained well during sixty days of treatment. After intravenous infection with highly virulent bovine organisms, rabbits developed no apparent miliary pulmonary lesions during seventy-one days' treatment; but their condition deteriorated less than ten weeks after treatment was stopped. (Swiss workers have just reported[8] that in guineapigs the parent substance

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1. *Quart. Bull. Sea View Hosp.* 1952, **13**, no. 1. See leading article *Lancet*, March 15, 1952, p. 547.
2. Elmendorf, D. F., Cawthon, W. O., Muschenheim, C., McDermott, W. *Amer. Rev. Tuberc.* April, 1952.
3. Benson, W. M., Stefko, P. L., Roe, M. D. *Ibid.*
4. Rubin, B., Hassert, G. L., Thomas, B., Burke, J. C. *Ibid.*
5. Robitzek, E. H., Selikoff, I. J. *Ibid.*
6. Bernstein, J., Lott, W. A., Steinberg, B. A., Yale, H. L. *Ibid.*
7. Steenken, W. jun., Wolinsky, E. *Ibid.*
8. Uehlinger, von E., Siebenmann, R., Frei, H. *Schweiz. med. Wschr.* March 29, 1952, p. 335.

is no less effective than combined streptomycin and P.A.S.)

The main report on the therapeutic effectiveness of this group of drugs is given by **Robitzek** and **Selikoff**. From their initial series of 97 patients, they have selected 44 for study of chemotherapeutic effect on acute progressive bilateral caseopneumonic tuberculosis. (They do not say what the results were in the 53 others.) The criterion of selection was that disease had progressed so far that the patient was no longer a candidate for any other standard accepted form of treatment. All but 3 had had other forms of chemotherapy previously, and had failed to respond. All were constantly pyrexial, had persistently positive sputum, and had lost weight during the pre-therapy course. In 39 the disease was regarded as far advanced, and on radiographic evaluation 31 showed progression during the pre-therapy course. The response to treatment of these patients, with daily doses of 1–10 mg. per kg. of the isopropyl derivative or the parent substance, was clinically dramatic. In 42 of the 44, the temperature subsided in two to twenty-one days. There was pronounced improvement in energy and well-being; appetite became "ravenous"; the average weight-gain was 19·7 lb. in an average of 8·8 weeks. The systemic response in these very ill patients was indeed remarkable: the erythrocyte-sedimentation rate, however, was unaffected. The response of the local lesion was less striking. In 8 the positive sputum was converted to negative. Radiologically there was no change in half the cases; in 17, cavities were reported to be smaller; in 5, the exudation seemed diminished. The report includes 6 impressive case-records, all of Negroes; it is noteworthy that in the series of 44 patients 8 were Negro, 7 Puerto Rican, and 29 white. The series treated at New York Hospital by **Elmendorf** et al. gave much less remarkable results: "it is not possible from the present observations to make any positive statement concerning the therapeutic value of this compound in the treatment of tuberculosis." **McDermott**,[9] commenting on this series, has stated that they were much less acute than the first Sea View series. He quotes Dr. **Robitzek** as saying that in the subacute and chronic forms of tuberculosis—the type one sees by and large in the sanatoria—the immediate results are not spectacular. He concludes that even in the very acute cases there is no way yet of knowing whether the impressive antituberculous activity will continue only for a few weeks, or whether it will endure.

On a later page we print a cautionary pronouncement by the Ministry of Health. Unfortunately sensational statements have appeared in the press, and no doubt more will follow. The drug is easy to take; and there will be a great temptation for physicians to prescribe it for all tuberculous patients, whether in hospital or at home. It is easy to make, and could soon be produced in large quantities. But in the U.S.A., where work has been proceeding since last July, general distribution of the drug has not yet been authorised, and it is to be hoped that the profession in this country will be not less careful. There are very real risks in using a drug before it has been properly evaluated; and it would be catastrophic if, as appears dangerously possible, it were to be procurable without medical prescription. We do not yet know the full range of the toxicity of this group, especially over long periods; we do not know whether the patient's tubercle bacilli may become resistant to the drug (resistant strains have been isolated in the test-tube). The American Trudeau Society[10] states:

> "Patients receiving the drug should be hospitalized for careful observation, and should be studied in institutions where not only potential toxic manifestations may be watched for most carefully, but where effects upon the course of the underlying tuberculosis may be carefully observed so that suitable alterations of therapy may be initiated when indicated. Routine laboratory precautions should include frequent blood counts and urinalyses, neurologic examinations and tests for renal and hepatic insufficiency."

We do not know whether the drug is equal in value to streptomycin, or better, or less effective; nor do we know how long its effectiveness continues. If the drug is really remarkable, the answers to these questions should be obtained rapidly. Comparison of the drug with streptomycin plus P.A.S. is already under way in clinical trials by the Medical Research Council, which are on a much larger scale than their previous trials of chemotherapy in tuberculosis. Individual physicians wishing to make a reasoned assessment of the drug might test it in cases where recent courses of streptomycin and P.A.S. have proved ineffective, and in sputum-positive cases with bacilli known to be distinctly drug-resistant. Use of the drug in these ways will lead rapidly to a far clearer picture of its place in therapy than can be obtained by its indiscriminate use. There is at present no certainty that isonicotinic acid hydrazide or its isopropyl derivative will accomplish more than has been accomplished with streptomycin and P.A.S.; it may prove to be an additional drug of great value.[10] While hopes may understandably run high, the most reasonable view at the moment is that of the physicians who made the first series of clinical observations —namely, that "it is believed that further investigation of the hydrazine derivatives of isonicotinic acid is warranted."

What Should a Nurse be Taught?

We run the wards of our hospitals very largely on the work of student nurses, and if all these young girls stayed in their profession we should soon have, not a shortage of nurses, but a glut. Their reasons for giving it up have been the subject of debate for the best part of this century, and the very fact that opinions on this topic vary widely shows the need for adequate research.

Many of the reasons suggested by The Lancet Commission on Nursing, twenty years ago, have now vanished: nurses *on the whole* now have good living quarters, reasonable hours, proper medical supervision of their health, lectures during (rather than outside) their time on duty, foreknowledge of their off-duty time, adequate meals, better pay, and something approaching student status. Yet the wastage—though not as high as it was during the war years—still continues. Material conditions being so much better, it is natural to turn to the content of the curriculum, and to wonder whether the heart of the trouble lies there. Dr. **Cropper** and Mr. **Houghton**, whose letter appears in our correspondence columns this week, feel quite sure that it does. They hold that a nurse's first duty is to make the patient comfortable, and that she does not need a lot of high-falutin anatomy and physiology to do that. Which is true. But it is also true that nowadays a nurse has other duties equally important, and calling for no little acumen, attention, and accuracy. If she is to collaborate intelligently with the doctor or surgeon using advanced methods she must have a good working idea of what they are doing and why. Moreover she has to use skilled techniques herself. As Sir SELWYN SELWYN-CLARKE put it, during a recent nursing recruitment campaign at Bath:

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[9] McDermott, W. Report at joint meeting of the tuberculosis sanatorium conference of Metropolitan New York and the New York Trudeau Society; March 5, 1952.

[10] American Trudeau Society. Statement on current status of isonicotinic acid hydrazide in the treatment of tuberculosis March 5, 1952.

> "Firstly, with the coming into being of the National Health Service in July, 1948, there has been a vastly increased demand for hospital services by the community as a whole. Secondly, the discovery of the sulpha group of drugs and of antibiotics like penicillin, streptomycin, aureomycin, and so on, has placed still more powerful weapons in the hands of the medical profession against diseases, some of which were often fatal in the old days. These and other means of treating disease, including surgery of the heart and blood-vessels, lungs, nerves and brain, and of dealing with injuries such as broken bones, severe burns and so on, combine to necessitate a much more elaborate nursing technique and, consequently, a larger number of nurses than before."

The subjects taught us in the medical curriculum have not all proved directly useful in later life. How many of us call on our botany and zoology? How many surgeons could now pass an examination in materia medica? How many physicians can recall the details of the anterior triangle of the neck? These studies taught us not facts, merely, but method—disciplined us in observation and accuracy, nourished a domineering professional conscience. Some such deliberate conditioning is as necessary for the senior nurse as for the doctor; and it will never be achieved by training her in nursing procedures alone. A girl of 18 with no grounding in science must be given a fairly stringent training in scientific method if she is later to manage such things as intravenous drips, the injection of potent or dangerous drugs, or the giving of pneumothorax refills. At the same time it is clear that not every girl who wishes to nurse is fit for this kind of conditioning. There are thousands—good bedside nurses, treasured by their patients—who could never achieve it. This is the problem which is at present confusing the issue, not only in Great Britain but all over the world. Miss LAWSON and Miss CARTER, on other pages, tell us how the United States and Canada are trying to solve it. The recognition that a proportion of nurses at least must be of a high intellectual and professional level has led the nursing authorities there to lay much emphasis—probably far too much emphasis—on university diplomas in nursing. Women so trained seem to be carried farther and farther from the patient in his bed; and he is attended more and more often by the orderly, the practical nurse, or the nursing auxiliary. Whatever name is given to these attendants, it always implies somebody with less than a "complete" nursing training. Sometimes these humbler workers are born nurses of the kind already discussed; sometimes they are not. But whether they are or are not, they have a sense of being second-grade, second-rate, and somehow inferior, just as our assistant nurses have.

Here is a situation created entirely by false values—almost class values—with no real meaning at all. Nurses can be classified as those who are capable of taking higher examinations and those who are not; or as those who have a natural gift for making people comfortable and those who have not; or as those who are capable of collaborating intelligently with a doctor and those who are not. These pairs of groups, unfortunately, are not coterminous. There are in each group women naturally suited for some types of nursing career and not for others; women capable of learning techniques for which they have no natural aptitude; and of course a few—though probably very few—who are not fitted for nursing at all. It seems perhaps unduly optimistic to put women varying widely in temperament, intellect, natural aptitude, and rate of learning through a single mill, and expect them to appear at the other end as a uniform product, wearing the label "nurse." This method loses us some of the most intelligent through boredom and some of the most naturally apt through ordeal by examination. The time has surely come, as Dr. CROPPER and Mr. HOUGHTON believe, for revision of the curriculum—though we do not fully share their views of what its new content should be. Every nurse should certainly be able to carry out those bedside-nursing procedures which are the very heart of the matter so far as the patient is concerned, and every nurse should be able to form a good and friendly relationship with her patients. But whether she is intellectually slow though naturally apt for such bedside techniques, or whether she is intellectually able though clumsy at blanket-bathing, she should be able to get the hang of them in less than three or four years. FLORENCE NIGHTINGALE taught them to simple women in a year; Canada has shown that it is possible to teach these techniques and *all the rest of the present curriculum besides* (though admittedly to picked students) inside two years. We hold to our oft-expressed belief that all student nurses should begin their career in the same way, with a simple direct course, lasting not more than two years, in the fundamental techniques of nursing. After that there should be infinite opportunities—nursing certainly offers them—for students to diverge along the paths in which their abilities will have most scope: some to remain at the bedside exercising a gift for that kind of nursing; some to go to the university to take qualifications that will fit them for the higher administrative and teaching posts; some to train for the highly important position of ward sister; some to train for public health or industrial nursing; and some to become midwives, health visitors, or district nurses. The opportunities and variety of nursing are so great that almost any type of woman can find rewarding work in it; and there should be no room for class distinctions among nurses, any more than there is among doctors.

"Promotion" is supposed to offer a difficulty; but surely this can be overcome by providing more chances of specialisation. In any team one member will covet one part of the task, another some other. Succession to a desired bit of work may be as satisfying as promotion; and members of a keen and happy team seldom ask to be "promoted" out of it: they are too intent on the job. Salary, of course, is a different matter, and in mere justice should rise with the seniority of the nurse.

Annotations

STILL NO APPLICANTS

FOUR months ago[1] we drew attention to the difficulty that some of the smaller and more isolated hospitals of the industrial North were having in finding junior medical staff. Now, as then, the total deficit is hard to assess, but some figures from the Manchester Regional Hospital Board[2] suggest that the position is getting no easier. What began as an administrative headache seems to be well on its way to becoming a real obstacle to efficient medical treatment.

Last November, it seems, the Manchester R.H.B. had 570 junior medical posts of which 417 were filled. Of the 153 vacancies 27 were for registrars (a deficiency of 19%), 64 for senior house-officers (29%), and 62 for house-officers (29%). These figures are discouraging enough; but, even so, their smooth statistical surface does not truly reflect the uncomfortable irregularities of real life. They do not show, for instance, how the comparative adequacy of staff in the teaching hospitals at the centre of the region is offset by really serious shortage in the hospitals at the periphery. Nor is shortage evenly distributed between specialty and specialty. General medicine is not so badly off, but general surgery, E.N.T. surgery, orthopædics, obstetrics and gynæcology, and anæsthetics are impoverished. The difficulties of the small hospitals are aggravated, too, by the unmathematical fact that a shortage of, say, 20% is more keenly felt in a small staff than in a larger one. To make matters worse, at this moment when young doctors are tending to move, or keep, to the centre, where prospects of promotion are better, the patients, as a correspondent has pointed out,[3] are making a resolute move to the periphery. In the long run this may help to right the situation by increasing the interest and importance of the work in the outlying hospitals, but it certainly increases present difficulties.

To meet their immediate needs the hospital management committee are being forced to employ locums, who prove expensive props, for some are asking as much as 15 guineas a week, to say nothing of free board and lodging. It has been suggested that, instead, more use might be made of general practitioners. But in the Manchester R.H.B. area they already contribute $1289\frac{1}{2}$ hours of work a week to hospitals as clinical assistants. Nor can they give exactly the kind of help that is needed to fill the gap. Save where they can be allotted specific duties—as in anæsthetics—general practitioners do not want to take on routine junior work. Nor are they, like resident staff, always at hand in emergency. Moreover their help is expensive in money; though it may pay good dividends in other ways. Thus the remuneration for two clinical-assistant sessions (7 hours per week including travelling time) is the same as the salary of a whole-time house-officer in his first appointment.

The suggestion that relief will come with the compulsory pre-registration year's training is received with some reserve by the Northern regions. They fear that the pre-registrands will still cluster round the centre, and that, once registered, they will be unwilling to go to a small hospital with anything less than the status of senior house-officer. Again, after the pre-registration year most of them will be anxious to complete their military service without waiting to spend a further year as a resident. And as soon as doctors have done their military service they usually want to go straight into general practice—partly because they need to earn money but also because they think it easier to become established in general practice if one has *not* held a registrarship. This is all the more regrettable because these peripheral hospitals often offer the best possible training for the future general practitioner: compared with the resident in the teaching hospital he has more responsibility and a less selected range of patients.

No easy solution to the problem seems to lie to hand. Local measures seem inadequate. A region is reluctant to ask its own teaching centre to restrict its junior posts if this benefits the larger hospitals of adjoining regions rather than its own periphery. This is a deficiency disease that seems to need a national rather than a regional remedy.

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[1] *Lancet*, 1951, ii, 973.
[2] *Northern Daily Telegraph*, Feb. 26.
[3] Poulton, E. M. *Lancet*, 1951, ii, 1141.

ELECTRONICS IN MEDICINE

As an aid to medical and biological research, the science of electronics has yet to be fully exploited. Even so, the cathode-ray oscilloscope has become a familiar laboratory, and even clinical, instrument; and electromyography and electro-encephalography have made us aware of the value of being able to detect and measure minute electrical potentials by means of high-gain amplifiers.

Several new techniques have been described in the past few months. We have been introduced to the idea of anæsthesia controlled automatically by the mean potential of the α-rhythm of the patient himself[1 2]; and the scope of electro-encephalography (E.E.G.) has been extended by Grey Walter and his associates,[2] at the Burden Neurological Institute, Bristol, who have devised a "toposcope" which shows frequency and phase relations as well as amplitudes. Each of twenty-two E.E.G. channels, fed by sixteen pairs of scalp electrodes, is connected to a small cathode-ray tube. Amplitude is apparent from the brightness of the tube, and the frequency is displayed by means of a radial vector rotating about the centre of the screen. If a signal of the same frequency as the rotational speed is applied to the tube, a sector of the screen is brightened. The fundamental frequency of the E.E.G. is found by altering the speed of the vector until a stationary sector appears. The phase relation is given by the relative "bearings" of the various sectors.

In a different field, Boyd and Eadie[3] have described a new heart-rate recorder for biological experiments. With this, as with similar instruments,[4] the electrical output from the heart, suitably amplified, triggers a circuit which produces for each heart-beat an impulse of constant duration and amplitude. After integration these impulses give a deflection, proportional to the heart-rate, on a meter from which a graphic record can be taken. Earlier instruments had various disadvantages; one of these was that the auricular and the ventricular beats could not be distinguished, and thus auriculo-ventricular block could not be recognised. It was found that these earlier circuits would respond to either the P wave or the R wave, and sometimes to the T wave. The problem was not solved until a frequency analysis of electrocardiographic records in the frog showed that the harmonic content of the R wave at about 15 cycles per second was usually much larger than that of the P wave, and always greater than that of the T wave. Hence, with suitable filters, it was possible to devise a circuit that was triggered by either the P wave or the R wave. This meter can be used only with anæsthetised or decerebrate animals; but Boyd and Eadie have now designed an instrument for clinical use.

Pressey,[5] formerly of the Nuffield Department of Anæsthesia at Oxford, describes an integrating and recording flowmeter which measures with reasonable accuracy varying flow-rates of mixtures for inhalation anæsthesia. The flow-rate is converted to pressure by means of a porous-plug transducer. The pressure is then measured by a capacitance manometer, thus avoiding the risk of explosion that would exist if a hot-wire anemometer were used. Volumes are measured by an electronic integrating circuit. The accuracy of the instrument is ± 3·5% for flow-rates from 0·05 to 3 litres per second, ± 2·5% for pressures from 1 to 50 mm. of water, and better than ± 6·5% for volumes of 0·1 to 75 litres.

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[1] See *Lancet*, Jan. 5, 1952, p. 40.
[2] *Wireless World*, 1952, 58, 72.
[3] Boyd, W. E., Eadie, W. A. *Electronic Engng*, 1952, 24, 102.
[4] Lundy, J. S. Clinical Anesthesia. Philadelphia, 1942. Horton, J. W. *Electronics*, August, 1938. Henry, F. *J. exp. Psychol.* 1938, 22, 598. Strum, Wood. *Rev. sci. Instrum.* 1947, 18, 711.
[5] Pressey, D. C. *Electronic Engng*, 1952, 24, 112.

Yet another interesting development is described by Molyneux.[6] In biology and physiology, it is often necessary to record information over long periods in order to observe some abnormality; and this leads to waste of paper or film. Molyneux has devised a circuit by means of which the records are made on magnetic tape; the interesting parts of the record can be stored on the tape or else transferred to a normal recording system. This method has the additional advantage that the time-scale of the recorded information can easily be changed; and that if ink-writers are used, their notoriously poor performance at high frequencies can be improved. In fact, their effective frequency response can be extended to 1000 cycles per second.

VARICOSE ULCERS

THE amount of attention that patients pay to their disorders depends partly on custom and fashion. Thus most people take a strain, or a sprain, or even a severe graze, quite seriously, and expect their doctors to do the same. A varicose ulcer, however, they accept almost fatalistically, dragging themselves round on their bad legs sometimes for years on end. So long as there is no bone infection, a few weeks in bed suffices to heal nearly every varicose ulcer; but rest must be absolute and the limb must be raised. Patients, especially women, are loth to give up this amount of time to the cure, and the only way to make them spare it may be to take them into hospital. It would be better still, of course, to prevent the development of ulcers; but this is not a particularly easy thing to do. Nobody expects an ulcer in advance. If varicose veins develop quickly and ache a good deal, patients usually come early for advice. Women sometimes come because the enlarged veins are unsightly, but unfortunately they are less often moved by this proper vanity than might be expected. If the veins develop slowly, over the course of 5, 10, or 20 years, patients often take little notice of them. In any case they seldom come asking how to avoid an ulcer unless somebody in the family already has one, and they have profited by the warning.

The hereditary factor in the development of varicose veins is strong. They are twice as common in women as in men, and the three periods of life in which they are most likely to appear are at puberty (a small peak), during childbearing (the main peak), and at the menopause (another small peak). Probably some endocrine factor at work at these stages of life favours varices. This idea is supported by the fact that in some women the veins appear only at the time of menstruation. During the childbearing period veins usually appear early in a pregnancy, during the second or third month; the weight of the uterus on the pelvic veins can therefore hardly be a factor producing them, and an endocrine cause must again be suspected. There is no evidence that poor diet has an effect either way. Ulcers develop when the skin has become congested and soggy, as a result of stasis, maintained by the action of gravity, and are thus naturally commoner in those who do a good deal of standing, never putting their feet up until they go to bed at night. The queueing housewife and the charwoman are common victims, and the initial injury which starts the ulcer may be quite trivial—a small abrasion or a mosquito bite, or the development of a local patch of eczema, will serve. At one time ulcers were rare in the middle classes; but now that relatively well-to-do housewives have to do more of their own shopping and housework, ulcers are probably getting commoner among them. The combination of factors in women which carries the worst prognosis is a bad family history of varicose veins, the onset of varicosities at or shortly after puberty, and the rapid development and progress of the varicosities with each pregnancy. Prevention depends on early and really efficient treatment of varicose veins—either by injection, by surgical measures, or by adequate support.

It is hard to know how to teach people to avoid ulcers, since the doctor sees only those who come complaining of veins, and if he does his part ulcers will never develop. Those who do not spare time to visit their doctors are more exposed to risk, and of course less accessible. This is one of the many subjects on which some medical education of the public would be useful and productive.

GENERAL CANTLIE'S RETIREMENT

Sir Neil Cantlie became director-general of Army Medical Services at a time of post-war reaction against everything military, and he had to accept heavy medical commitments without having enough officers. He tackled these responsibilities with the resolution and courage expected of him, and by wise distribution of his resources he was able to prevent the breakdowns that might easily have occurred. The introduction of the National Health Service increased the difficulty of recruiting officers into the Royal Army Medical Corps, and the D.G.'s strenuous and persistent efforts to obtain better rates of pay for doctors in the Service brought an inadequate response from the financial authorities which has made it no more easy to obtain potential specialists: but we may still hope that his endeavour to improve the position of officers of the Corps will bear fruit. He has also set in motion no fewer than six investigations into other means of increasing the efficiency of the medical services. The committee concerned with nursing has made recommendations that should go a long way to make the work and career of nursing officers more attractive, and in the past two years female other ranks have been successfully introduced as part of the Q.A.R.A.N.C. Perhaps one of the most important innovations during the period has been the institution of a Field Training School, at Mytchett near Aldershot, through which all National Service officers and other ranks, as well as short-service and regular personnel, have to pass; and each year since General Cantlie took office he has held a four-day medical exercise for senior officers at this school, from which many valuable lessons have been learnt. Other reforms concern the issue and distribution of medical supplies, in which greater efficiency and economy have been attained.

No director-general has done more than General Cantlie to further the professional side of the Corps: the teaching at the Royal Army Medical College has been widened, and the instruction given in the larger military hospitals has led to some of them being recognised as suitable for candidates for higher qualifications. Similarly, no D.G. has been in closer personal contact with his officers. In his difficult task he has shown a drive and energy that has never flagged, and even within his last few months of office he has undertaken a strenuous visit to the Far East, with visits to Japan and front-line units in Korea. In what is sure to be an interesting form of retirement he carries the good wishes of those who have served with him and under him. To Lieut.-General Frederick Harris, who succeeded him last Tuesday, we wish an equally successful if less troubled reign.

Sir LEONARD HILL, F.R.S., formerly professor of physiology at the London Hospital, and subsequently director of the department of applied physiology at the National Institute for Medical Research, died on March 30, at the age of 85.

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[6] Molyneux, L. *Ibid*, p. 130.

Special Articles

CANADIAN NURSING

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VISITING LECTURER TO THE UNIVERSITY OF TORONTO SCHOOL OF NURSING, 1948–50

THE character of general hospital care is changing. The traditional idea of a bedfast patient, given loving care by nurses, in which such procedures as bed-baths and frequent attention to pressure points figure largely, is disappearing everywhere except in long-stay wards. Patients get up early, they move about, and they go to he toilet instead of having a bedpan. They choose heir own food and can often go to a dining-room for a meal instead of having it in the ward. Perhaps most mportant of all, they know more, and expect to be told more, about their illness. The mental aspects of nursing, he mental component in every physical illness, what we now describe as social medicine, the realisation that omeone might have prevented the illness, and that nyhow the patient must be taught how to prevent its ecurrence, or how to live with his disability—all these actors show up the inadequacy of the training of nurses n the one hand and the limitations on their field of ction on the other.

Moreover the spread of education is doing away verywhere with the uneducated group of cheap labour who can be called in to do what the better educated or the more privileged do not wish to do. There must be team-work; and within the team of course there must be grades, based on skills and carefully safeguarded by public egistration, but the best results will be obtained only if every member, however humble, is shown the part he has to play and has some conception of the goal. There must also be flexibility within the team, so that the exceptionally able or gifted woman, or man, can be ransferred and trained for more skilled employment. This is particularly necessary in countries where the tandard of education is low and where educational opportunities are restricted, although the level of ntelligence may be high.

THE NURSE WITH A UNIVERSITY DIPLOMA

Canada has done much to spread what one might call professional consciousness. By bringing nursing within the university she has made a postgraduate course in Canada an objective to nurses from many countries. This is particularly true of the University of Toronto School of Nursing, which has for many years had a large group of international students, but it also applies to other university schools of nursing in the Dominion. It was my impression that what the students gained was not so much professional techniques as the illumination given by the teaching of such subjects as sociology, psychology, and mental hygiene, which they learn along with students from other faculties. The idea of the university school for women who have already taken an ordinary nursing qualification is gaining ground in other parts of the world: Heidelberg, for instance, is to have a university school of nursing with a German nurse at its head who has been a Rockefeller student at Toronto.

Someone will immediately say, “ Yes, but what about nursing the patients ? ” My own feeling was that because nurses were able to look with greater detachment on the whole question of the prevention and cure of disease, they began to see more clearly the means which might be necessary to bring nursing care in its widest sense to the people; they could see the complexity of the question, and the need to make use of men and women from all walks of life. It was a great gain for Canadians and others to get together within the framework of the university to discuss these questions. It should mean higher standards of skill and devotion, not lower.

THE BASIC NURSING TRAINING

I got the impression that the Canadian Provincial Professional Associations, who are entrusted with the registration of nurses, are readier than we are to change and adapt curricula for the basic nursing qualification to changing needs. Ontario, for instance, has made a period of psychiatric nursing a compulsory part of the curriculum this year. Provincial Associations are prepared to sanction experiments. This usually means that all the Provinces consent, since reciprocity between provincial registers is usual. The most notable is the demonstration sponsored by the Canadian Nurses Association (representing all Canada), and financed by the Canadian Red Cross, to show that a two-year period of training, during which nurses are students and not paid employees, is adequate for teaching not only the basic skills but the preventive outlook. It is now drawing to a close and the results are being carefully assessed and evaluated. Students pay for their training and are selected from every part of Canada; a minimum educational level is required (junior matriculation). The school, directed by Miss N. Fidler, at which the students live, is an independent educational institution with its own practice rooms and laboratories. Students go to the Metropolitan Hospital, Windsor, Ontario, and to other institutions for clinical experience and have their own teachers with them. The concepts of preventive medicine and the practice of public health are fully integrated with the general training. Successful completion of the course admits to the Ontario register, though it does not confer a qualification in public health. A student wishing to qualify as a public-health nurse takes a year's postgraduate course at a university school of nursing. Recently the Western Hospital, Toronto (600 beds and a training school) has started a two-year course, also sanctioned by the Nurse Registration Department of Ontario. Graduates of this school, unlike the Windsor graduates, are required to do a third year as paid internes, at a Red Cross outpost hospital or other hospital.

THE UNIVERSITY-TRAINED PUBLIC-HEALTH NURSE

After the first world war Canada began to revolt against the three-year apprenticeship system of training, on the ground that it was insufficient to give the nurses the training they needed to do the job as they were faced with it in the Dominion. Departments of public-health nursing were therefore started in Canadian universities, financed by the Canadian Red Cross. In Ontario, the University of Toronto assumed financial obligation for the department in 1923, and it was transformed in 1933, with the support of the International Health Division of the Rockefeller Foundation, into the University of Toronto School of Nursing with Miss E. K. Russell as its director. At this school, in addition to postgraduate courses in public health and nursing education, and the courses in clinical supervision, designed to make clinical teaching in wards and departments more thorough and realistic, constant experiment in the content and length of the basic course went on. From the beginning the students were not the employees of any hospital.

Completion of a course of 39 months entitled the student to registration as a nurse in Ontario and gave her a recognised qualification in public-health nursing. This in itself was a great achievement, making public health an integral part of the course, and not something added after hospital training. This basic course met the needs not only of Canadians, but of others, notably Latin Americans, several of whom, as Rockefeller scholars, took it and returned to give help in the building up of nursing and public-health services in their own countries.

The 39-month diploma course has now been given up. It was replaced by a four-year course, now lengthened to a five-year course, leading to the degree of B.SC.N. conferred by the University of Toronto. Throughout the five years academic subjects, such as history, English, and basic sciences, studied in company with students of the faculty of arts, are taken, as well as the technical nursing subjects. The student does her clinical practice at the Toronto General Hospital and other institutions, under the direction of teachers from the school of nursing. On qualifying, she is a graduate of Toronto University, a graduate nurse, qualified in bedside nursing and a qualified public-health nurse.

Canada has also recognised that adequate care of patients, especially of the old and long-stay patients, can only be accomplished by training other categories of worker. The Registered Nurses Association of Ontario took the initiative in experimenting with the training of nursing assistants. The provincial government then established schools for nursing assistants, who complete a 9-month course (as students and not as employees), and are then enrolled on a special register and work in selected hospitals under the supervision of registered nurses. Similar courses have been approved in other provinces.

THE WILL TO EXPERIMENT

Canada is a vast underdeveloped, underpopulated country with immense natural resources awaiting exploitation. During recent years the Federal Government has come to realise that health problems transcend provincial boundaries and increasingly large funds are allocated to the health services, including the nursing services.

Registered nurses are strongly organised federally as well as provincially and they are well placed to advise the Canadian government. My impression is that Canada is out to solve her problems in a big way; that the public at large, as well as the nurses themselves, are fully aware that the nursing aspects of the total health problem require a number of women of outstanding ability. It seems logical and right that they should take their place in the universities, not to become academic figure heads, but, as Sir Francis Fraser[1] has said, to acquire culture, a sense of values, and a joy in the use of the intelligence, no matter what practical skills may be learned in addition. They will thus be fitted to take their part in solving the world-wide problem of how to offer to all the best chance of mental and physical well-being.

Every country in the world is nowadays aware that we have the knowledge at least to attempt this project; but economic and cultural revolution is necessary if it is to come within reach in measurable time. Great Britain seems to have gone farthest along the road towards its realisation, and every country would like to follow suit if it knew how; but everywhere the cost of *treatment* is mounting. In Great Britain and in all the countries of the west, the hospital provides the traditional way of dealing with ill health. If the less developed countries follow the traditional hospital pattern they will be brought up against the barrier of cost just as we are. The obvious way of reducing expenditure on hospitals and curative medicine is to prevent illness, and above all mental illness; but neither the public, the doctors, nor the nurses, know much about how to do this. What seems clear is that the problem can only be solved by group activity and the team approach; for only a team can give the patient everything he needs. Nurses everywhere want full membership of the team, and the chance to use all the brains and skill they possess.

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[1] *Lancet*, 1952, i, 61.

NURSING AND NURSE EDUCATION IN AMERICA

M. G. LAWSON

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I HAVE recently visited Canada and the United State under the auspices of the Rockefeller Foundation, an have had an opportunity of studying methods of nurs training. In both countries more and more importanc is being placed on the possession of a university degr (B.SC.) in nursing, and there has been a considerabl expansion of collegiate and university schools of nursin

The pattern of these, both in length and content (the curriculum, tends to vary somewhat.

According to the *Wayne University* (*School of Nursin Bulletin*[1] "hundreds of positions calling for the universit prepared nurse are vacant and opportunities for such wome are *growing rapidly*: *to care for the acutely ill* and to supe vise the care given by practical nurses; to teach in schoo of professional and of practical nursing; to supervise an administer nursing services; to work in all types of position in the rapidly expanding fields of public health . . . ne opportunities are opening in child guidance centers, ment health clinics, and home follow-up programs, as well as i treatment units of mental hospitals. Because service need are so great, several studies have been made *recently pointin* to a re-organisation of nursing education in the United State Universities are urged to assume responsibility for the educa tion of professional nurses, just as for workers in all othe professions."

About 10% of nurses are college graduates and abou 10% of schools of nursing are administered by college and universities, giving a planned programme combinin general and professional education.

EMPHASIS ON PUBLIC HEALTH

In, I think, 5 university schools of nursing in the U.S.A and in the Toronto University School of Nursing, th basic professional programme prepares the nurse fo staff positions in both public health and institutional nursing, emphasis, according to the *Bulletin*, being placed throughout the curriculum on "total needs of patients; upon the family and community health aspects of care; and upon an understanding of the mental as well as the physical health needs of patients." The aim of this type of preparation for nursing is explained *thus*: "While the university program includes excellent preparation for a career in the direct care of patients, the program is designed primarily for those interested in, and capable of, finding their careers in teaching, supervision or administration."

The basic training for registration as a general trained nurse in both Canada and the U.S.A. requires a period of experience in obstetric nursing, and in psychiatric nursing. Where the hospitals to which the school of nursing is attached or in which the students from university or collegiate schools obtain their experience, cannot themselves provide experience in these specialties, affiliations are arranged with other hospitals sometimes at considerable distances from the parent institution. *Hospitals* may, therefore, have many groups of students from different schools of nursing gaining practical experience or undertaking "supervised practice" in their wards.

For example, the new Children's Hospital at Toronto has 600 "*affiliated*" *nurse students passing through it* every year (i.e., 150 every 3 months) from 35 affiliating hospitals. In addition, it has its own student nurses and those from other children's hospitals who are undertaking the major part of their nurse training in sick children's nursing. There *are no supplementary registers for sick children's* nurses, or for mental trained nurses as we have in this country, but nurses wishing to specialise in these branches of work may spend 2 years in the special hospital, and *1* year in a general hospital at the end of which they take the provincial or state examination for "registered nurse" (R.N.).

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[1] 1951, 29, 30.

DEGREES IN NURSING

In Canada, about 15 schools of nursing carry a degree rogramme. At the University School of Nursing in Toronto, the course lasts $5^{1}/_{2}$ years, and the measure f liberal education which the university considers ssential to a first degree is closely integrated throughout he course with the professional training in nursing. The hospital training is controlled by the school of ursing. The more usual pattern is, however, that a irl completes 2 years of college or university education, nd then undertakes 3 years' hospital training, at the nd of which she obtains a B.SC. degree in nursing. Both groups take the Provincial Examination for egistration as a nurse. In the U.S.A. about 110 schools f nursing have courses connected with a university r college, which give a degree in nursing. In a few f these, integration of the academic and professional raining is carried out throughout the course, which is enerally 4–$4^{1}/_{2}$ years in length; but in the majority he 2-year plus 3-year pattern mentioned above is ollowed.

SHORTENED COURSES

Hospital schools of nursing in both countries give a diploma in nursing after a 3-year course. Two interesting modifications of this were seen in Canada:

1. The school of nursing attached to the Metropolitan Hospital, Windsor, Ontario, is an experimental school, inanced by funds from the Canadian Red Cross Society, and conducted by the Canadian Nurses' Association. This has been a 4-year experiment "to demonstrate, if possible, that a skilled clinical nurse can be prepared in a period shorter than 3 years, once the school is given control of the use of the student's time." The course has been a 2-year one, and the 4-year experimental period finishes about September, 1952. An independent evaluation is now being undertaken which will be of considerable interest.

2. In September, 1951, Toronto Western Hospital started a 2-year period of training to cover the full theoretical and practical requirements for registration, followed by a third year of contract in the wards and departments of the hospital, during which the student gives $7^{1}/_{2}$ hours service daily for 6 days and has half an hour daily of clinical or other instruction. The examination for registration is taken at the end of about $2^{3}/_{12}$ years, but the certificate is withheld until satisfactory completion of the third year. The student nurse receives no payment during the first 2 years and pays a nominal tuition fee of $50. She is paid a $100 per month (less than half the usual monthly salary of the trained nurse) during the third year, and during this final year she pays for her room, maintenance, and uniform. From September, 1951, a grant of $150 per student nurse is being paid from Federal Funds to the nursing school for an experimental period of 5 years. This scheme is also designed to prove that nurses can be educated in a shorter period of time if there is adequate control and use of their time for educational purposes.

SUPPLEMENTARY GRADES OF NURSES

None of the schools of nursing which I visited had its desired complement of student nurses, and there is an acute shortage of trained nurses for staff nurse positions, i.e., for actual bedside care. Many more nurses are engaged in private nursing than in this country. Qualified general duty nurses usually work morning, evening, or night shifts. In many instances it is necessary to pay a bonus, over and above the agreed salary, to induce nurses to undertake the evening and night shifts, and the bonus is higher for evening work than for night duty.

There appears to be a considerable amount of movement of general duty nurses between different posts. The frequent changes of personnel must create a real problem for supervisory staff. Deficiencies in trained staff are made up by the employment of non-professional auxiliary nursing staff, which includes practical nurses and nursing-aids. In some cases the number of aids equals that of the trained nurses, and in consequence a good deal of actual nursing duties must be delegated to them. These aids receive a short "in-service" training in the hospital which employs them.

Neither in Canada nor in the U.S.A. is the nursing assistant or "practical nurse" as fully used as she might be.

In Canada she has 9 months' training of which the first 3 months is theoretical. In the U.S.A. the theoretical period is generally 4 months, followed by 8 months hospital work. I understand that there are also many unofficial training schemes, and in January, 1951, only 4 States and 1 territory provided for mandatory "licensure" of this group, although in a number of states, "licensure" was permissive. This grade is intended to include the older age-group up to 50 years of age in some schools. When qualified, the practical nurse can earn about three-quarters of the salary of the trained nurse. The reluctance to make full use of this grade of worker, who, it is envisaged, must work always under the supervision of the trained nurse in hospitals or agencies, is difficult to understand, since increased numbers would probably greatly help the staffing shortages.

THE NURSING TEAM

Contrary to our custom, the tendency seems to be to relieve the head nurse (ward sister) of more and more direct responsibility for actual patient care. In most cases, she is also relieved of the duty of teaching student nurses by the appointment of clinical instructors in wards. Her function is conceived as a dual rôle—"to represent the nursing service and hospital administration to the patient, and to represent the patient and his needs to the administrative groups." The nursing team, as far as the patient is concerned, seems to start with the staff nurse. Very extensive use is made of clerical assistance on the wards, and in some instances, there is also a ward housekeeper and a ward dietitian.

The extent to which the student nurse is encouraged to regard the teaching of her patient and his family as an important aspect of treatment was interesting. This is undertaken both in the wards and outpatient departments and includes both the prevention of illness and social and environmental factors having a bearing on ill health. We realise, in these days of psychosomatic medicine, that anything that adds to the patient's mental or physical comfort has a considerable effect on the course of his illness, and this is stressed throughout the whole of nurse training.

EXAMINATIONS AND TEACHING METHODS

Examinations for registration of nurses are completely objective and there are no practical or oral examinations. All the States use a standard series of tests which are compiled by the Department of Measurement and Guidance of the National League of Nursing Education, but each State fixes its own pass mark. A group of tests is a formidable document which takes 18 months to 2 years to compile and which is then used for about 2 years. Candidates are supplied with special answer papers on which they are required to tick off the square which corresponds to one of a series of answers which they consider the best or correct one. The human factor is eliminated in arriving at the score, since all answer papers are evaluated by machine. It is claimed that the student's ability to make the right judgment in a given situation is tested with quite as much accuracy as in the essay type of examination, and better than in the thoroughly artificial atmosphere of the practical examination room.

The cost of nursing education is high, since few students receive salaries during training, and many pay high fees for tuition and for residence. The nursing profession itself in America is in favour of Federal aid for nursing education, but has not so far succeeded in having the necessary legislation passed.

An interesting development has been introduced at Vanderbilt University School of Nursing where the student nurses, from the middle of the second year onwards, are *employed* by Vanderbilt University Hospital for 12 hours per week over and above the 24 hours per week which they spend on the wards in supervised practical nursing. They are paid at the rate of 90 cents per hour, and this helps to pay for their residence in the school of nursing. They work one week-day evening from 7 to 11 P.M. and 8 hours consecutive duty on Saturday or Sunday. The idea of working to pay for university education is of course a common one in America, and indeed is appearing in other countries; but the large number of students who take part-time university courses, and thus have to spread their period of academic work over many years, is striking.

In schools of nursing the formal courses of lectures from doctors in medicine or surgery, to which we are accustomed, are replaced by what is called an "integrated program."

A group of diseases—e.g., diseases of the respiratory system or a specific condition such as peptic ulcer—is chosen, and students are given two or three lectures by the physician on ætiology, signs and symptoms, and medical treatment. The dietary management and therapy is given by the dietitian; drugs used in the treatment of the conditions by the instructor in pharmacology; surgical treatment by the surgeon, and nursing procedures, including those which are special to the conditions under consideration, by the nursing instructor. No attempt is made to consider individual diseases; the idea is to teach principles capable of application to a group of diseases, and to help the student to work out for herself what modifications must be introduced where deviations from accepted principles are required.

PUBLIC-HEALTH NURSING

On the whole, teaching of student nurses is conducted much more by group discussion and presentation of original work by the students than is usual in our nursing schools. For this, they have to read widely and lead discussions on material which they have prepared. They express themselves freely and well. For all this, it is doubtful whether their method of training prepares them to accept responsibility as readily at the end of it as we expect. It was interesting to learn that in those schools of nursing which prepare for both hospital and public-health work, rather more than half the students elected to take up hospital work in preference to public health nursing, and some students were quite frank in saying they did not feel ready to assume responsibility. There is a tendency for the degree nurse to be forced into responsible positions at an early stage, because hospital and other authorities appoint them in preference to nurses holding only diplomas from hospital schools. Many of them are absorbed into the large teaching faculties which are attached to the schools of nursing, and it is doubtful whether any great number undertake actual bedside nursing. This would appear to be one of the reasons for the instability of the staff nurse grade in hospitals, since there must be a sense of insecurity among those who do not possess a degree, and a realisation that they are unlikely to obtain the higher teaching or administrative posts, unless they acquire a degree by postgraduate study.

Most public-health nurses are trained for this branch of work by taking a year's postgraduate course for the special certificate. Those working in the visiting nurse associations or agencies combine home nursing with public-health teaching in the homes. Those attached to community health centres and to State health departments undertake health teaching in the schools as well as in clinics. The view is held that the salaries paid in public-health work are not high enough to attract the nursing-school graduate, particularly in view of the additional training usually required.

The public-health service of the Federal Security Agency in its Nursing Resources Division has a staff of nurse consultants in both the public-health and hospital fields. Their services are available on request to States to make surveys of their nursing needs, to advise in staffing and equipment of hospitals, and so on. They also conduct research into problems concerned with nursing. Eight such surveys were made during 1951. According to the annual report of the Federal Security Agency,[2] "These aim to define the problem (nursing shortage) within the State, discover ways to improve the resources for nursing education, and stimulate the communities on a State-wide basis to solve the problems delineated." They are said to have had many concrete results, and in every State surveyed "some kind of council or committee is now putting into effect the recommendations of the survey." Schemes to deal with recruitment of nurses on a regional basis have been planned in four areas.

"Through its Public Health Nursing Division," the report goes on, "the Public Health Service provides leadership and guidance in the development of this basic activity. The staff furnishes direct consultation services to health and nursing administrators, participates in the work of numerous organisations, and directs or aids in surveys of public health nursing needs and problems. The staff also assists State and local health agencies in establishing or improving their nursing programs."

The more one saw of nursing problems and difficulties across the Atlantic, the more one realised how closely they matched our own. While the ways of our Canadian and American colleagues in dealing with them may not always be suited to our rather different circumstances, nothing but good can come from seeing along what lines they are working. One of the things which impressed itself upon me on this, my first visit, was the extreme friendliness with which I was received, and the readiness with which they admitted a colleague to their counsels. The many informal talks with students and professional nurses in all fields of nursing were of great value in giving me an insight into what they are striving to achieve.

Public Health

A STUDY OF TUBERCULOSIS IN A CORNISH DISTRICT

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OF conditions which favour the spread of pulmonary tuberculosis, the most important is contact with an infectious case. Turner (1932) showed that in North Worcestershire the mortality from pulmonary tuberculosis among contacts was 8 times that of the normal population and the morbidity was 16 times as great. The Prophit survey (Royal College of Physicians 1948) showed the morbidity in contacts to be 6 times that of a control group.

The attack on tuberculosis should follow the normal epidemiological approach to any infectious disease—namely:

1. Careful assessment of the general environment and of the incidence of the disease, with uncovering of cases not notified.
2. Determination of the source of infection of individual cases, and isolation, instruction, and treatment of patients so found.
3. Protection of susceptible members of the population exposed to infection, and improvement of their environment.

For such an attack, the artificial barriers which separate prevention and treatment of illness must be broken down: the chest physician, general practitioner, local health authority, mass-radiography unit, and epidemiologist must undertake a combined operation.

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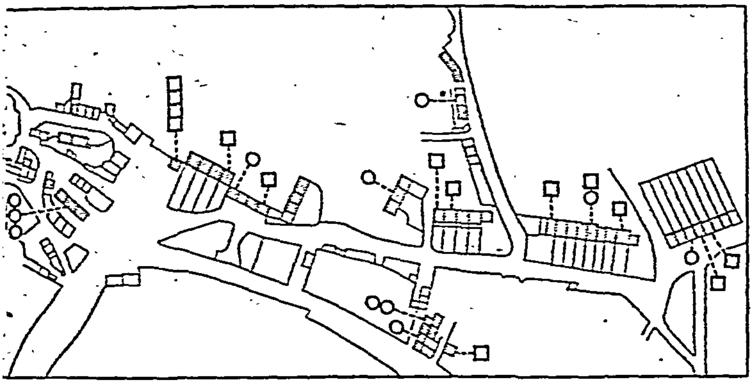
[2] Annual Report, Federal Security Agency, 1950. Public Health Service.



ig. 1—Tuberculosis cases in a village, since 1925. The circles represent living patients, the squares deaths. Houses are shown by shaded squares.

In Cornwall we recognised that no active measures ould usefully be taken to discover new cases unless here were hospital beds for the cases found. On the ther hand, even with the small number of beds available, great deal can be done by speeding up the turnover. arly diagnosis with early admission should shorten he stay in hospital and open the road to domiciliary reatment.

To facilitate early discharge we now visit the homes of ll patients admitted to the sanatoria, and take action to nsure that the home is not overcrowded and that the patient an have a separate room on his return; if necessary, a helter is provided. We also make certain that adequate ome nursing is available; if necessary a home help is also upplied. All household contacts under the age of 40 are lantoux-tested, and negative reactors are vaccinated with .C.G.

For public-health administration Cornwall is divided nto seven areas, each with a population of about 50,000. n intensive antituberculosis campaign may be expected o produce about 3 cases requiring a hospital bed per 1000 of the population; therefore if 100% of the opulation in one area of the county were examined, pproximately 150 cases would be revealed.

The shortage of beds and staff made an attack on this scale impracticable; it was therefore decided to launch a campaign on one local authority area, extending the work into adjacent areas as opportunity permitted.

THE AREA INVESTIGATED

When deciding on which area to start, it was tempting to tackle the problem geographically, starting in the Land's End peninsula and working progressively eastwards; second thoughts suggested that the greatest good could be done by beginning where the incidence was highest. Maps were prepared showing the comparative incidence and comparative mortality of tuberculosis in local authority areas within the county. Both incidence and mortality rates varied considerably, but high rates were confined to only 3 or 4 of the 30 local authorities in the county. The place finally chosen was the urban district of St. Just which has a tuberculosis incidence more than 100% above the mean for the county (5·5 per 1000 on Jan. 1, 1950). This district, which has a population of 4076, is divided for electoral purposes into two wards—St. Just Churchtown (population approx. 2500) and Pendeen ward (population approx. 1500). The former consists of the town of St. Just and the latter of little clusters of houses (Carnyorth, Trewellard, Pendeen, and Bojewan) which straddle the main road as it passes north along the coast towards St. Ives. The town of St. Just, once a prospering mining centre, has now no staple industry. One tin mine, Geevor, some three miles to the north, is still working, and many of the men who live in this part of the urban district are employed there.

The tuberculosis register contains 54 names in the St. Just urban district, 46 being pulmonary cases and 8 non-pulmonary.

The homes of these patients were visited and in each case a brief appreciation made to assess the home conditions and decide, where possible, the source of infection and necessary action. These investigations were greatly facilitated by the whole-hearted co-operation of the general practitioners in the area. The families visited, without exception, gave me every assistance—much useful information being supplied from family Bibles.

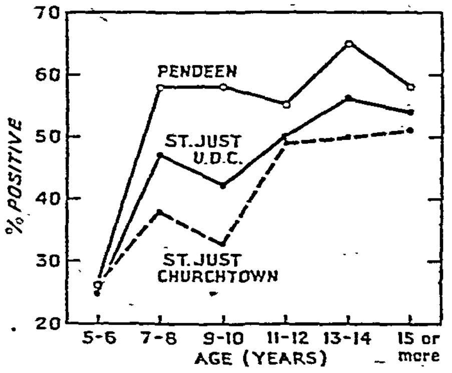


Fig. 3—Conversion-rates at different ages of children in the district and its two wards.

The incidence of disease through the area is by no means even. The figures for the two wards are:

	Pop.	No. of cases	Incidence per 1000
St. Just Churchtown	2500 ..	19 ..	7·60
Pendeen	1500 ..	35 ..	23·30

Certain blocks of houses appear to be heavily infected. Thus in the 58 houses of Boscaswell village there are 11 known cases, and there have been 16 deaths in the past twenty-five years (fig. 1). In the Pendeen ward the cases were largely confined to the descendants of four or five families; fig. 2 shows the pedigrees of two of these families. In nearly half the known cases the patient was 40 years of age or over.

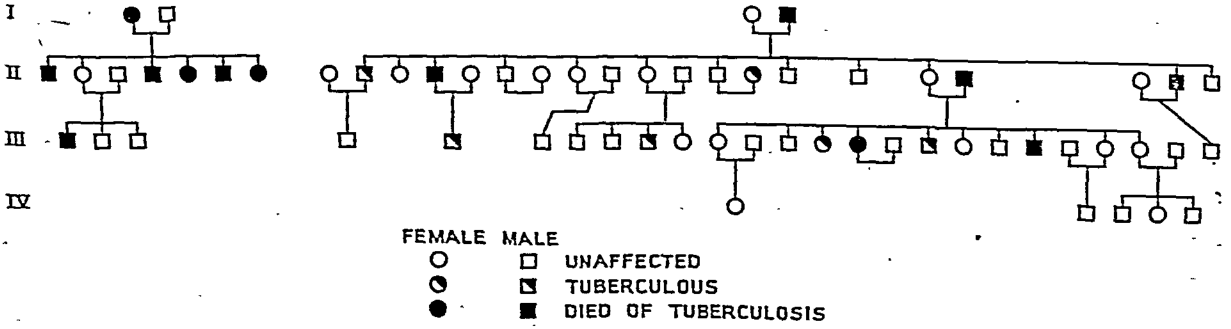


Fig. 2—Pedigrees of two tuberculous families.

TUBERCULIN TESTING

A tuberculin test was offered to all children attending schools in the area. The parents were approached by means of a circular letter for permission to carry out tuberculin testing, and the response was excellent, 92% accepted.

Tuberculin jelly was used, the method being that advocated by Pointon Dick (1950). To ensure uniformity, the application and reading of the tests was done by a team of one health visitor and two doctors. Positive reactors were graded according to sensitivity into + (slight), ++ (moderate), and +++ (severe).

The results are shown in table I and fig. 3. No correlation was found between the degree of sensitivity and subsequent X-ray findings. It is interesting to note the consistently higher spontaneous conversion-rate in children of the Pendeen ward than in those of St. Just Churchtown.

TABLE I—RESULT OF TUBERCULIN TESTS

Age (years)	St. Just Churchtown		Pendeen		Total (St. Just U.D.C.)	
	No. tested	Positive %	No. tested	Positive %	No. tested	Positive %
5–6	23	26	31	26	54	25
7–8	47	38	34	58	81	47
9–10	61	33	38	58	99	42
11–12	59	49	20	65	79	50
13–14	72	50	9	66	81	56
15 and over	39	51	12	58	51	54

MASS RADIOGRAPHY

We were fortunate in obtaining the services of a mass-radiography unit for six weeks, and the director with his team worked very hard to make the project a success. The aim was to radiograph the largest possible proportion of the whole population, except children under 5. The survey was undertaken between Jan. 29 and March 15—admittedly too early in the year, but the unit was committed elsewhere for the summer. The usual methods of advertising the presence of the unit were employed—namely, posters, letters, talks with local organisations such as the British Legion and Women's Institutes, and a house-to-house canvass. I am indebted to Dr. Geoffrey Sheers for permission to publish his figures. Table II shows the response and table III the significant results. Among the inactive groups are included many small calcified foci of no clinical significance.

TABLE II—RESPONSE TO MASS RADIOGRAPHY

Group	Totals	No. available†	No. radiographed	% radiographed
School-children ..	524	365	294	80·54
Geevor Mine	310	310	216	69·67
St. Just U.D.C. (totals)	4093	3615	1611*	44·5

* 105 were X-rayed at hospital.
† 319 children under 5, and 159 tuberculin-negative school-children aged 5–11, were excluded.

B.C.G. VACCINATION

It is now generally believed that B.C.G. gives some degree of protection to the susceptible and can rightly be given to contacts and those exposed to special risk.

The parents of tuberculin-negative children in the St. Just area were asked whether they would like their children to receive B.C.G. vaccine should it be considered necessary. The response was good: 82% accepted, 6% refused, and 12% did not reply to my letter. Vaccination has so far been limited to contacts of known cas all of those willing have now been vaccinated.

TABLE III—CASES FOUND

	No. of cases	*Incidence pe 1000 exam*
Pulmonary tuberculosis:		
Active	12	7·9
Observation	13	8·6
Inactive	171	113·0
Silicosis	31	20·6

DISCUSSION

Certain aspects of this survey have been disappointin particularly the response to the offer of mass radiograph Early in the investigations St. Just became labelled b the press as a "black spot," a description much resent by the local council; and, though the small bette informed section reacted in a rational manner, man stayed away for fear that "something might be ther Better to live in ignorance than to know."

Much has been achieved. We now know the locati of most of the dangerous sources of infection; we ha an X-ray record of the school population, together wi the record of their tuberculin reactions; and we ha the coöperation of parents to carry out B.C.G. vaccinati where necessary. We have the promise of mass rad graphy in St. Just for three or four days yearly— time long enough to allow annual examination of children aged 11+. This has all been achieved by t use of the resources on the spot—the general prac tioners, the health visitors, the district nurses, and t school medical officers. We have therefore, I feel, evolv a practical method which can be used in other parts of t county.

There are, I believe, strong grounds for extendi B.C.G. protection. Anderson et al. (1951) emphasise th when vaccination is confined to contacts, many childr are missed who subsequently develop tuberculosi and that natural tuberculin conversion occurs main in the age-group 15–25. He therefore advocates t use of B.C.G. for all school-leavers. In an area such St. Just, where the incidence of tuberculosis is hig conversion apparently occurs soon after entry to scho and, should this finding be confirmed, it would reasonable to use B.C.G. early in school life.

SUMMARY

As an intensive attack on tuberculosis cannot made along the whole front, it was decided to concentra efforts in areas where the incidence is highest.

An account is given of the activities in the first ar tackled.

The St. Just urban district contains some 4000 peop 92% of the school-children have been tuberculin-test and those found to be positive have been radiographe Of the "available" population (3615) some 45% ha been radiographed.

During the survey, 25 active or observation cases tuberculosis were discovered and 171 non-active cases, o of a total population of 1611.

All tuberculin-negative contacts who are willing ha been vaccinated with B.C.G.

I should like to thank Dr. R. N. Curnow, county medic officer for Cornwall, for permission to carry out the survey a for his helpful advice; his staff at County Hall for prepari the illustrations; Dr. W. K. Dunscombe, the medical offic of health of the no. 1 health area; and the practitioners the area for much useful information and active assistance.

REFERENCES

Anderson, A. W., Grenville-Mathers, R., Trenchard, H. J. (195 *Lancet*, i, 1116.
Dick, P. (1950) *Brit. med. J.* ii, 141.
Royal College of Physicians (1948) Tuberculosis in Young Adult Report of Prophit Survey (1935–44), p. 148.
Turner, H. M. (1932) Ministry of Health Report on Tuberculos p. 164.

Isonicotinic Acid Hydrazide

The Ministry of Health has issued the following tement:

'The favourable reports from America suggest that nicotinic acid hydrazide may represent a considerable vance in the chemotherapy of tuberculosis. This drug, refore, certainly needs to be fully investigated; but the same time, even on present evidence, it is clear t it would be unwise to use it indiscriminately. It is no means certain that it is harmless; indeed, animal periments indicate the possibility of toxicity, partiarly when the drug is used for a considerable time. man little or nothing is known of long-term toxicity. other strong reason against indiscriminate use is the ssibility of developing resistant strains of tubercle cilli in the community. Nothing is known of this in n yet, but it is known that such strains can develop the laboratory.

" It would seem prudent for the present to limit its to the treatment of inpatients in such hospitals as equipped with a full laboratory service."

The G.P. and the Health Visitor

One of the less publicised aspects of the National alth Service has been its reaffirmation of the family the unit of medical care; and the City of Birmingham one of the forward-looking bodies which have been sitive to this reorientation. In the duty laid upon alth authorities under the N.H.S. Act of providing alth visitors to advise the family unit, Birmingham ve seen an opportunity for closer coöperation with e general practitioners; and "closer coöperation" not an empty phrase, for the council are prepared make important alterations in the structure of their alth services.

Dr. Matthew Burn, their medical officer of health, s pointed out that the medical officer of the family it is the general practitioner, and that logically the alth visitor should now become his aide instead of ing based on a municipal clinic. Dr. Burn therefore inks it unnecessary for the city to build more maternity d child-welfare centres of the type previously built. stead he suggests that, at first as an experiment, their new housing areas the city council should carry t their responsibilities under the Act by arranging r their health visitors to join forces with the doctors actising in the area. But not only will the general practioners use the health visitors in their surgeries, they ill also be free to hold their antenatal and postnatal inics at the city's maternity and child-welfare centres.

Dr. Burn believes that the by-products of this proposal ill be efficiency, economy, and good will. The scheme as the further advantage that it may well prove to e a foundation on which the hoped-for health centres f the future can be built. These proposals have been ccepted by the health committee of the city council nd by the local medical committee on behalf of the eneral practitioners. They are shortly to come before he whole city council for confirmation, and they will hen be referred to the Ministry of Health.

Variola Minor

Up to the start of this week the outbreak of variola ninor in England remained confined to Rochdale and he surrounding districts except for a young soldier, nfected at Rochdale, who has developed the disease at ldershot, with onset on March 14 and admission to ospital on March 17. In Lancashire the only district ewly involved in the week ended March 29 was Bacup, rom which 1 case was reported. A further 16 cases vere notified during the week ended March 29, making total this year of 126. There have been no deaths.

". . . The people one should really aim at keeping out of the hospitals are not doctors but patients."—*Manchester Guardian* leader, March 26, 1952.

Medical Conferences

ADVANCES AGAINST CANCER

THE Second National Cancer Conference, sponsored by the American Cancer Society, the National Cancer Institute of the U.S. Public Health Service, and the American Association for Cancer Research, was held at Cincinnati, Ohio, from March 3 to 5. The programme was divided into clinical and research sections; but this was fortunately not a rigid dichotomy. The clinical section consisted of seven panels: breast, genito-urinary tract, head and neck, lymphomas and leukæmias, female genital tract, gastro-intestinal tract, and lung. The fifth National Gastric Cancer Conference was incorporated into the panel on gastro-intestinal cancer. The research section also consisted of seven panels: radiobiology, genetics, cytology, chemotherapy, isotopes, virology, and steroid endocrinology. In addition two general sessions were held each day. Finally, two informal round-table conferences were held: one on the Significance of Statistical Analysis in End-results of Treatment of Breast Cancer; and the other a joint meeting of the breast, genito-urinary, female genital tract, and steroid endocrinology panels, at which the ætiological rôle of endocrines in the genesis of human tumours, the response of cancer to endocrine therapy, and the methods of changing the hormone balance in the human were discussed.

Clinical Section

THE BREAST

End-results.—The informal round-table discussion on the Significance of Statistical Analysis in End-results of Treatment of Breast Cancer provoked a lively interchange of viewpoints. Most of the discussion dealt with the recent controversial paper by Park and Lees.[1] These workers had claimed that it had not been proved that the survival-rate of cancer of the breast, using the 5-year survival-rate as an index, was affected by treatment at all, and that examination of published reports showed no direct evidence that delay in treatment diminished the cure-rate. J. C. LEES (Kingston upon Thames) stoutly defended his thesis, as did N. E. MCKINNON (Toronto), who had reported[2] similar observations.

It seems that general agreement on this subject is unlikely to be reached until large numbers of comparable cases have been accumulated and carefully analysed statistically; to this end the American Cancer Society has undertaken to act as a clearing-house for breast cancer data reported by the method recently adopted by a joint committee of the American Cancer Society, the American College of Surgeons, the American College of Radiologists, and the College of American Pathologists.

Nipple Discharge.—D. A. JACKSON (San Antonio, Texas) reported observations on the cytology and significance of nipple discharge—i.e., secretion expressed from the nipple. This was found a useful technique for detecting intraductal papilloma (a lesion regarded as premalignant), but was not a test for cancer; in cancer, secretion was usually unobtainable owing to involvement of the duct system. Of 160 cases of intraductal papilloma discovered and operated on between 1942 and 1949, 63% were revealed by examination of nipple discharge. C. M. POMERAT (Galveston, Texas) said that sheets of epithelial cells were formed in vitro (tissue culture) from papillomatous clusters that had been obtained from breast secretion, and he showed a film of the appearance of the cells under phase-contrast microscopy.

Operative Technique.—O. H. WANGENSTEEN (Minneapolis) described a "super-radical" operation for breast

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1. Park, W. W., Lees, J. C. *Surg. Gynec. Obstet.* 1951, 93, 129.
2. *Canad. J. publ. Hlth*, 1949, 40, 257.

cancer in patients with axillary lymph-node involvement. In addition to conventional radical mastectomy, the supraclavicular lymph-nodes and the parasternal lymph-node chain are removed; the lymph-node-bearing tissue in the anterior mediastinum is also dissected. A somewhat similar procedure was described by J. A. URBAN (New York), who had operated successfully on 31 patients within the last twelve months. The value of this procedure will not be known until more operations have been performed and the patients followed for longer periods postoperatively.

Other Methods of Treatment.—Bilateral ovariectomy for pre-menopausal patients with inoperable or recurrent breast cancer was recommended by G. W. HORSLEY (Richmond, Virginia). I. T. NATHANSON (Boston) discussed steroid hormone therapy for advanced breast cancer, recommending œstrogens post-menopausally, and androgens pre-menopausally; androgens could also be given post-menopausally, but had more profound effects on bone lesions in pre-menopausal cases. In most instances, unfortunately, a favourable response to hormone therapy was relatively short.

THE LUNG

Early Diagnosis.—The importance of early diagnosis of lung cancer received much attention. R. H. OVERHOLT (Boston) emphasised that the "cancer potential" of the so-called silent lung shadow (X ray) was so great that exploratory thoracotomy in such cases was well worth while; tumours at this early stage were invariably resectable. In providing wide intrathoracic and thoraco-abdominal exposure, ribs need not be resected or fractured, or their heads avulsed. Mortise-and-tenon fixation provided a practical way to reunite ribs that required division; normal thoracic cage rigidity was immediately restored, and permanent röntgenologic deformity of the bony structures avoided.[3]

L. W. GUISS (Los Angeles) and R. J. ANDERSON (Washington, D.C.) stressed the importance of mass-radiography surveys for detecting lung cancer, particularly at the vital "silent shadow" stage. A practical lung-cancer control measure would consist in radiographic examination of the chest twice a year for men over 40, and prompt investigation of any lesions detected in this way.

Vagus Resection.—K. P. KLASSEN (Columbus, Ohio) reported that he had performed unilateral vagus resection as a palliative measure in 53 cases of non-resectable bronchogenic carcinoma. The vagus was severed, just below the recurrent laryngeal nerve, at the time of exploratory thoracotomy. Life was not prolonged, but the patients were more comfortable as distressing cough was absent in most cases, and deep chest pain of vagus origin was abolished; no adverse effects following vagus section were noted.

GASTRO-INTESTINAL TRACT

Repeated Operation.—O. H. WANGENSTEEN (Minneapolis) said that re-operation (the "second-look" procedure) on the lymph-node-positive cases, particularly in cancer of the colon, was sometimes of value; indeed, he had, on occasions, not hesitated to have a third, fourth, or even further "looks" for eradicable metastases.

Photofluorography as an aid to the early diagnosis of gastric cancer was discussed by R. D. SLOAN, R. H. MORGAN, and J. J. WOLFSON (Baltimore), and by R. WIGH and P. C. SWENSON (Philadelphia). The latter group reported that this procedure was an inexpensive cancer test with single-organ specificity, high accuracy, and a low false-positive rate. As more gastric adenomas were found than would have been expected in conventional röntgenologic work, this lesion was regarded as a silent precursor of cancer. Wigh and Swenson felt that photofluorography had thus more to offer than chemical tests since these, even if successfully developed, were not expected to detect benign lesions.

Gastric Analysis—Another approach to the diagnosis of gastric cancer was reported by H. L. SEGAL, L. L. MILLER, and J. J. MORTON (Rochester, N.Y.), who discussed the detection of achlorhydria by "tubeless gastric analysis."

They used an ion-exchange indicator ('Diagnex-QH'). H ions from gastric HCl displace the quinium cations of this indicator, quinine HCl is formed, absorbed mainly from the small intestine, and subsequently excreted in the urine; the amount of quinine in the first two hours' urine secretion after administration of the indicator determines the presence or absence of free gastric HCl.

Of 505 patients over 40 years of age "screened" in this way, 67% had achlorhydria, and this was confirmed by intubation of 23 of them selected at random.

Clinically, there appears to be a positive correlation between achlorhydria and gastric cancer. J. BERKSON and M. COMFORT (Rochester, Minnesota), however found no [illegible]nce that in a group of 850 patients [illegible] observed for 10 years, the incidence of gastric cancer differed from that in the general population.

GENITO-URINARY TRACT

Bilateral adrenalectomy for advanced cancer of the prostate or the breast was discussed by D. M. BERGENSTAL and C. HUGGINS (Chicago), who reported 35 operations, the last 31 being without mortality. Of 9 patients with advanced prostatic cancer, previously treated by castration and given stilbœstrol, who had been submitted to adrenalectomy, significant remissions were observed in 5, 2 showed appreciable improvement, 1 was not improved, and 1 died. Among the evidence of regression of the lesions were gain in body-weight, increase in plasma-proteins, decreased percentage of thermocoagulable protein of serum, decrease of elevated serum acid-phosphatase, increased hæmoglobin and red-cell content of the blood, and shrinkage of size of the tumours. Relief of persistent crippling bone pain was an outstanding feature. The results of this procedure in advanced breast cancer are still equivocal as only 11 patients have been treated, and these within the last ten months; of these 11, 3 are dead; but of the remaining 8, 5 showed significant response. Apparently bilateral adrenalectomy is well tolerated by man, and maintenance therapy of about 25 mg. of cortisone acetate twice daily, and an extra 3 g. of sodium chloride daily in the diet, give excellent results postoperatively.

Other Operations.—Further heroic operative procedures for advanced cancer were reported by W. W. SCOTT (Baltimore), who had removed the pituitary from a patient with advanced prostatic cancer (this man is alive and doing quite well on cortisone maintenance therapy); by L. PARSONS (Boston), who thought there was a place for Brunschwig's pelvic exenteration operation for advanced cancer of the cervix although the mortality in his cases was 34%; and by D. B. MORTON (Los Angeles), who felt that meanwhile pelvic exenteration was a procedure to be offered rather than advised.

Uterine Carcinoma.—The results and prospects of telecobalt irradiation in carcinoma of the uterus were discussed by G. H. FLETCHER (Houston, Texas) and also by C. B. BRAESTRUP (New York). Compared with conventional 200–250 kV X rays, telecobalt had the following advantages: the depth dose was higher; the naximum ionisation occurred in the subcutaneous tissues; md the relative absorption in bone compared with soft issue was less. Braestrup felt that if and when C^{60} was eadily available it would probably be preferred to X rays for high-energy radiation.

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[3] Overholt, R. H., Kenney, L. J. *Surg. Gynec. Obstet.* 1952, 94, 305.

Malignant Melanoma.—G. T. PACK (New York) mphasised that moles in the genital area or on the soles f the feet should be removed since these were the most ikely sites for the development of malignancy in a itherto benign mole; ultraviolet light, filtered through Vood's glass, was of value for detecting tiny moles in hese areas. Malignant melanoma commonly metastasised o the heart, and electrocardiography was useful to detect uch spread.

Exfoliative Cytology.—J. F. SEYBOLT and G. N. 'APANICOLAOU (New York) mentioned one interesting levelopment in this field—the so-called balloon techique. A specially designed balloon covered with a ough net is passed into the stomach and inflated, and he peristaltic waves carry it towards the pylorus. The et is subsequently washed in a beaker, and sediment mears are fixed, stained, and examined. H. L. RICHARDSON (Portland, Oregon) described the technique f collecting, preserving, and examining smears from he vagina, bronchi, sputum, stomach, œsophagus, ectum and sigmoid colon, prostate, urine, kidney, reast, oral and pharyngeal cavity, as well as certain ther body tissues; he also described the gelfoam urface sponge biopsy technique.

EXPERIMENTAL SECTION

A. HADDOW (London) discussed the potential significance of recent developments in the study of mechanism f carcinogenesis.

A. E. MOORE (New York) reported some fascinating xperiments on oncolytic viruses and their adaptation o tumours. Certain viruses were found to have a definite ffinity for some types of tumour tissue and were able to lestroy tumour cells. The virus of Russian encephalitis, for example, attacked sarcoma 180, an experimental rat tumour. Several viruses were screened for oncolytic activity; each oncolytic virus appeared to have its own "tumour spectrum" in that it might attack one type of tumour and not another. Further, certain neurotropic viruses, by multiple passage through specific animal tumours, increased their destructive capacity for tumour cells; neurotropic activity for mouse brain was not, however, lost in these experiments. C. P. RHOADS (New York) described some of the extensive studies now being made in an effort to apply these findings to the treatment of human cancer.

P. R. PEACOCK and S. BECK (Glasgow) reported the current position of their search for possible dietary carcinogens, with special reference to strongly heated (350°C for 4 hours) cottonseed oil. Although addition of this substance to a balanced diet under varying conditions induced squamous papilloma or carcinoma of the mouse forestomach, no trace of any of the well-known carcinogens was observed after chemical fractionation and analysis of the oil.

J. G. KIDD (New York) discussed the progression of Shope-virus-induced rabbit papillomas to cancer (the so-called V2 cancer); the papilloma virus per se did not appear essential for the continuing malignancy of the V2 carcinoma cells. Thus the Shope virus could be regarded, along with tar, sunlight, arsenic, 20-methylcholanthrene, and so on, as a carcinogenic agent—i.e., one which changes tissues so that cancers arise in them—but plays no part in the continuing malignancy of the cancer cells.

L. R. C. A.

In England Now

A Running Commentary by Peripatetic Correspondents

IT was a surprise to be told by a highly respectable and intelligent lady of 76 that she knew from experience what "drunkard's thirst" is like. She is a connection of mine by marriage whom I have only lately come to know well, but I was certain that her life has been one of blameless innocence and that she never touches alcohol. She explained. For a time in her youth, roughly between the twenties and thirties, she suffered from intense thirst which nothing could quench. It came in bouts, and she was in effect a dipsomaniac, though the fluids she drank were only water, tea, coffee, and such like. I asked whether she passed correspondingly large amounts of water, but she could not remember. She had never consulted a doctor about it, and in time the attacks passed off. We agreed that if she had been a man, or had lived in a different environment, she might well have taken to drink in the usual meaning of the word. Even now she drinks three cups of tea to my modest one and twice as much of other liquids. Apart from a tendency to bronchitis, a loose cartilage in one knee, varicose veins, and partial paralysis of the mouth and throat left by poliomyelitis in early youth, she is hale and active for her age; but of her dipsomania she says gloomily, "I'm sure it is because my father took drugs." Her father was a parson who became addicted to laudanum, taken at first for the relief of pain. Her mother died of tuberculosis when my friend was a year old and had never held her baby in her arms.

Had there been some transitory pituitary dysfunction to account for her thirst, or was it purely psychological—a thirst for the mother's milk she never had? Mind-body being what it is, perhaps both were factors.

* * *

I really have been a bit peripatetic lately, having flown across and round the continent of America in my search for truth or such variants of that commodity as can be found in the medical schools there. So I think I am qualified to tell you something of the American predilection or preference for the shower-bath versus the "tub-bath."

This is of great importance to planners of hospitals—and especially to planners of nurses' hostels—in this country. Here in England we planners think, or at least hope, that we can persuade male medical students and male residents to use a shower. The use of a shower results in an enormous saving of water, of power to raise water, of fuel to heat water, and of metal for tanks to store water. The saving of expense represents a really very considerable sum of money every day. But, as we sit in our planning committees with these aquatic statistics before us, we are told by those who should know—Matron and experienced hospital architects—that nurses in this country simply will not use showers.

It is interesting therefore to record that in America, generally speaking, both nurses and doctors regard the tub-bath as a primitive and insanitary method of washing. As one doctor said to me, "You get out of a tub-bath covered with a dilute fæcal solution." While I regard this as an over-statement—an expression of the American obsession which amounts almost to a *folie de laver*—it would be a good thing, and a convenient thing from the point of view of hospital planners, if nurses in this country would at least "have a go" at mastering the technique of the practical, economical, and hygienic shower-bath. You really can, I am assured, effectively protect your "perm" by means of a plastic cap.

* * *

Somehow the announcement that we've got our forty million at last did not give me the feeling of exhilaration I had expected. That came next morning when an enterprising salesman sent me a list of secondhand Rolls-Royces and Bentleys. I suppose my reactions are slow, for at the time I merely switched off the wireless and went on with my job of helping our daily turn the drawing-room carpet, in hopes that if the settee covered a bare spot it would last another few years. Later that evening I did toy with the idea of ringing up my garage to ask whether my new car, ordered back in the '40s, was likely to materialise before the summer. But I didn't want to flaunt my newly won wealth in the garage man's face; so I tied a knot in my handkerchief to remind me to get some car polish and left it at that, deciding to spend the few minutes before surgery time in accustoming myself to being a person of means. But only one thing became clear—that we have lost our pet grouse. I can no longer pass the time at any more tedious private visits in swearing at the N.H.S., the B.M.A., and the Minister. I shall have to listen to my patients' own troubles instead. That may be better medicine, but I've got out of practice in the last four years and shan't enjoy them.

* * *

Has anyone done a time-and-motion study of the removal of pennies from a money-box? I do not mean one of those new-fangled contraptions with lock and key, but a stern uncompromising money-box cast in stout metal, with no concessions to human frailty beyond a forbiddingly narrow slot. The withdrawal of large irregular objects through narrow and ill-adapted orifices is a familiar problem to the proctologist and obstetrician; but their orifices are to some extent dilatable, whereas the money-box slot is rigid enough to baffle even a neurosurgeon. In view of the lack of recent literature on what is, prima facie, a surgical emergency, I am offering the fruits of my own experience in one consecutive case.

The operator should lie in the Trendelenburg position holding the box upside-down over his chest. An E.N.T. surgeon's head-lamp is an advantage at this stage, for it enables the presenting part to be clearly visualised. Perhaps I should here disabuse the beginner of the idea that the viscus necessarily contains money. Its physiological contents are pennies, half-pennies, and farthings, but almost equally common are pathological inclusions such as trouser-buttons, dead matches, pieces of 'Plasticine,' and torn up postcards. The presence of safety-pins usually indicates malignancy.

In the initial exploration, brisk succussion will define the extent and probable duration of the operation. Indeed, it may bring on a brief overflow incontinence, which must not be mistaken for evacuation of the viscus. If the operator is not to leave a residue of unknown nature and amount, the passage of an instrument is always necessary. The size of the slot is a limiting factor, but the blade of a kitchen knife is most generally suitable. This is manœuvred inside the box, at first gently and then more vigorously, after the fashion of a leucotomy knife. In the present case half an hour's manipulation of this kind yielded 1*s.* 9¾*d.*, with a standard deviation of ± 1·5 trouser-buttons. The impulse to reach for a lithotrite or cranioclast when faced with such a return must be sternly resisted. On the other hand, a small magnet can be safely used to remove small ferruginous foreign bodies, such as coupling-hooks from a model train, which so often precipitate an acute retention.

* * *

"Evidently it is possible to gild the lily." This opening remark in a book-review of March 15 (p. 546) can be dealt with as it deserves because of the anonymity in which THE LANCET still cloaks its reviewers.

Imprimis: The phrase's pseudo-literary connotations do not commend themselves to me. *Item*: It conveys an inaccurate impression of what follows, implying useless embellishment, whereas valuable amplification is in fact meant. *Item*: It is needless to inform the enlightened readers of these catholic selections that the lily is painted, gilding being reserved for refined gold.

* * *

News from School.—"In siesta yesterday we each took mirrors on our beds and dazzled people going up the road by making queer noises and then pointing lights on to them. We dazzled an aeroplane (?) and it flew down out of control (?) and only just missed the prefabs at the bottom of the garden. It didn't really, but it could have done. . . . I have had a thought about my birthday but I'm not sure about it. How poor are we?"

Letters to the Editor

WHAT SHOULD THE NURSE BE TAUGHT

SIR,—May we put to you, as we see them, so problems of nursing education? To us, there *is* no sh age of nurses other than that artificially created by t responsible for the nursing curriculum. The keys to situation seem to be:

1. Nursing employment should be available for leaving school who wish to nurse.
2. The nursing curriculum should be limited to mat truly relevant to a nurse's duties.

Headmistresses have told us that an apprecia percentage of girls leaving school at the age of 15 "nursing" as their first choice of a career; but f economic necessity these girls usually drift into indus We need a country-wide scheme of employment for leaving school before the age of 19, whereby they ca absorbed at once into hospitals where they should once earn a wage which offers an incentive. (Exampl the successful operation of this scheme may be seen in Birmingham region.) Graduated tasks should be provi for them which would relieve the trained staff of som their duties and introduce the cadets to nursing degrees. The gap between school and the prelimi training school would thus be filled. Incidentally, preliminary training school itself needs reform. I too long, too theoretical, and probably of all stages most irrelevant and the most disliked.

Secondly, we think the present lectures and exam tions entirely inappropriate. They seem designed turn girls with little or no basic scientific education poor imitations of medical students. We contend nurses do not need to know the physics of radiother nor the prognosis of acute nephritis (these are ac subjects of lectures). The General Nursing Council, matrons and sister-tutors, the doctors who lecture nurses, and the writers of textbooks for nurses' use ar to blame for this foolish excess of science in their cu culum. In an 800-page textbook on surgery for nu we *found a long paragraph on the laboratory* techni of the Zondek-Aschheim test and 11 pages on X- diagnosis.

One reason for the ridiculous curriculum is the com tition between nurses and nursing auxiliaries. As group extends its syllabus so do the others. Consi the assistant nurse: she has had a training far prolonged and arduous. Yet many physicians and geons will testify that her ability and usefulness ma those of the fully qualified girl, and, where her voca is clearer, that she surpasses many a State-quali nurse in devotion and professional capacity. Experie therefore belies the necessity for the present elabo curriculum. The demands of our own nursing exami result in a high wastage through discouragement damage to health. The student nurses are tired inarticulate, and their grievances never boil up into organised protest.

Doctors have no leisure to recast their lectures, they base their teaching of nurses on the lectures t have already given to medical students. Patients nei need nor want to be nursed by nurses with this kin knowledge. The nurse should know a circumscribed ra of facts and techniques germane to the craft of nurs Much of her knowledge is not strictly the concern the doctor, just as much of his is emphatically not concern of the nurse; each is complementary to other. The greater part of the nurse's education sho be in the minutiæ of ward-management.

The nursing course should be drastically pruned at least a year cut out of it. At the same time it ne to be thought out afresh, and to have new matter inc porated in it—such as elementary common-sense psyc ogy, which would enable the nurse to teach patients the art of accepting illness. Anyone who has been warded knows that what the patient asks of the nurse is an indeinable quality of personality which makes her more than a technician. She should be able to make the patient feel that she is sharing the burden of his illness while remaining detached from it. Attention to this nurse-patient relationship is a first call on the education of nurses: the fact that those responsible for nurses' training have turned themselves into crammers of facts to be memorised shows how far they are removed from the realities.

C. F. J. CROPPER
PAUL HOUGHTON.

Worcester.

PREVENTION OF CORONARY THROMBOSIS

SIR,—I was aware of the studies by Tropeano and Prosperi, cited by Dr. Sbarigia (Feb. 2), on the influence of α-tocopherol on blood coagulation. We have warned[1] that a fresh thrombosis may develop in a patient taking a large dosage of α-tocopherol; but we added that increasing the dose slightly will resolve that thrombus promptly. We have repeatedly seen this happen. The proper dosage is the dosage that is effective; and, of course, it may not coincide with our first estimate.

Dr. Sbarigia could have readily found reports by Italian workers[2] who have pronounced α-tocopherol very useful in coronary disease. Let Dr. Sbarigia try it for himself; nothing is easier to settle than whether or not it can quickly resolve a fresh thrombosis. Then he and we may hunt for the explanation at our leisure. Quinine and a hundred other drugs were used by doctors long before their modus operandi was discovered.

Shute Institute,
London, Ontario.
W. E. SHUTE.

AN UNUSUAL EPIDEMIC

SIR,—I have been interested in your annotation (Feb. 9) and in the subsequent correspondence.

Vertigo is not uncommon in this part of the country. The usual sequence in the cases I have seen is sudden severe headache, associated with vertigo and sometimes nausea and vomiting, usually coming on after waking in the morning. The symptoms are sometimes so severe that the patient is unable to lift his head from the pillow. Examination reveals no obvious disease of the ear, nor is there evidence of infection; the temperature is usually normal or only slightly raised. Nystagmus is usually absent or doubtful. Two features are, however, fairly constant—namely, the headache, which is usually hemicranial, and accompanying tender points in the suboccipital region. I have in many of these cases obtained immediate and lasting relief from an injection of procaine or 'Metycaine' into the tender point. The effect is dramatic. If care is taken to make the injection into the actual tender point, which is sought with the point of the needle and usually found on the surface of the aponeurosis, 2 ml. of anæsthetic is sufficient.

In my opinion these are cases of fibrositis. In many of these cases of headache hyperæsthesia of the scalp is felt when the hair is combed; this hyperæsthesia was noted by me in 51% of 87 cases of fibrositic headache. It is analogous to the hyperæsthesia of the thighs met with in cases of lumbago and sciatica of fibrositic origin, and is an example of Lewis's nocifensor manifestation.[3] There would seem no reason why this hyperæsthesia should not affect the vestibular system and produce vertigo.

As regards the epidemic nature of the malady, I have had the impression for many years that fibrositic disease—headaches, lumbago, pleurodynia—do appear in waves of increased incidence; and I have often wondered whether the Bornholm syndrome is not merely one manifestation of an epidemic of fibrositis. It would be interesting to hear the views of other practitioners on this point.

Dartmouth.
R. M. S. MCCONAGHEY.

ABDOMINAL INJURY FROM A CRICKET-BALL

SIR,—In the U.S.A. Gonzales[1] has lately described a case in which the patient died from a non-penetrating abdominal wound by a cricket-ball. The following case had a happier ending.

A man, aged 33, was admitted to this hospital on Sept. 25, 1948, with a history of having been hit in the abdomen by a cricket-ball $4^1/_2$ hours previously. Since the injury he had experienced severe upper abdominal pain and had vomited once. On palpation of the abdomen there was generalised board-like rigidity with maximum tenderness apparently in the epigastrium and right iliac fossa.

At operation on the evening of admission the abdomen contained free fluid, which was turbid; there was a $^3/_4$ in. tear of the antimesenteric border of the terminal ileum, which was repaired in layers. There was also further evidence of contusion of the small gut just distal to the perforation. The abdomen was closed without drainage. The patient made an uninterrupted recovery, and was discharged on Oct. 8.

It would be interesting to know how common such cases are in this country.

Hackney Hospital,
London, E.9.
R. F. READ.

THE NEW TREATMENT FOR TUBERCULOSIS

SIR,—One has seen many messiahs come to the tuberculous and fade away—garlic, creosote, and cacodylate and gold. But none has had such good credentials as isonicotinic acid hydrazide, with its respectable background of laboratory and animal experiment, with its record of improvement in 90 cases of advanced tuberculosis, all of whom put on weight and became afebrile, some of whom ceased to have tubercle bacilli in the sputum, and some of whom displayed that clinical rarity—the large dry cavity. As you said on March 15, it has made an excellent debut.

The point of this letter is to ask what is being done in this country for large-scale production and extensive trials.

It would be nice to suppose that when the Minister of Health's attention was drawn to the half-column on the important page in the *Times* of Feb. 23, headed "New Drugs for Tuberculosis," he said to his staff:

> "By Jove, this concerns me very much. I am responsible for a hundred thousand patients with tuberculosis. We'll send Dr. Hook and Dr. Crook over by air tomorrow; they can cable back their report, then we can have a conference with tuberculosis officers and manufacturers next week, and arrange for extensive trials."

That is the degree of urgency that, to anyone not habituated to the thought of thousands of men and women coughing away life, the situation would seem to demand. Remembering, however, the paralysing fairness of the official medical mind, so often indistinguishable from inertia, I do not think this sense of urgency can be taken for granted in the circles where it is most needed. Perhaps our medical M.P.s will stimulate it with shrewd questioning. They must not be put off with "The matter is still very much in the experimental stage and the Ministry is keeping a close watch on the whole question." We are not interested in what they are watching but in what they are doing.

It may be suggested that the drug is not without its dangers; but the six months of the American trials do not seem to have disclosed anything more than trivial drawbacks. Because a drug has a remarkable action in a disease it does not necessarily mean it is potent in other directions—e.g., that fraction of vitamin B which does the miracle in beriberi. Secondly, it may be suggested that there is no hurry. But that statement would not appeal to the army of people who are being excavated by the tubercle bacillus. Besides, it would show a complete absence of the urgencies of humanity without which the "scientific, detached mind" can become an evil.

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[1] Shute, E. V., Shute, W. E. *Amer. J. Surg.* (in the press).

[2] Butturini, U. *G. Clin. med.* 1950, 31, 1. Mantero, O., Rindi, Trozzi. *Atti Congr. Cardiologia*, 1949. Galeone, A., Minelli, M. *Minerva med.* 1950, 46, 694.

[3] Lewis, T., Kellgren, J. H. *Clin. Sci.* 1939, 4, 47.

[1] Gonzales, T. A. *J. Amer. med. Ass.* 1951, 146, 1506.

Beckley, Rye. C. G. Learoyd.

TENSION PNEUMOTHORAX FOLLOWING TRACHEOTOMY

Sir,—I was interested in Mr. Bauer's helpful letter (March 15). The sole point of my article, however, was to draw attention once again to this very dramatic, lethal, tension pneumothorax coinciding with the dislodgement of the tracheotomy tube from within the lumen of the trachea; and to bring out the fact that mere replacement of the tube is not sufficient to save life.

The only way of *preventing* this calamity is to make the tracheotomy as high as possible, and not to fix the tube with the neck extended. If it is fixed with the neck extended there is a considerable risk that when the child flexes his neck and the trachea sinks into the chest, the tube will be left behind, as it were, and will slip out of the hole in the trachea. The fatal sequence of events will then be set in motion.

Park Hospital,
Davyhulme, Manchester. John Dark.

CAT-BITE FEVER

Sir,—The case described as "cat-scratch fever" by Dr. Garai (March 29) was caused by the bite of a kitten, and therefore appears to be one of "cat-bite fever." Dr. Garai says that it seems to be the first recorded case in England. In 1935 I described with Dr. Morton Gill a case of cat-bite fever which responded in a remarkable way to intravenous injections of N.A.B.[1]

London, W.1. G. E. Beaumont.

PANCREATICOGASTROSTOMY

Sir,—I would like to support the contentions of Professor Wells and his colleagues and of Mr. Dill-Russell (March 22) concerning the implantation of the pancreatic stump into the stomach.

I came across this procedure quite accidentally when performing an excision for carcinoma of the head of the pancreas in October, 1950. It struck me that the parts seemed to fall together easily, and the substance of the stomach wall lent itself to suture more easily than the jejunum. Although the patient was 71 years of age, he made an uneventful recovery; and he died nine months later from metastases. The stump of the pancreas was simply inserted into a small incision on the posterior wall of the stomach, using a treble layer of no. 40 cotton sutures. I have lately had cause to regret not using this procedure in another case, where the patient died from a fistulous leak three weeks after I had implanted the pancreatic stump into the jejunum.

I would like to make a plea for bringing up the jejunum and implanting the common duct end-to-end, rather than using a loop of the jejunum with an end-to-side anastomosis. It is quite simple to divide the jejunum just distal to the duodenojejunal flexure and to "dislocate" it from underneath the superior mesenteric vessels. The cut end of the jejunum seems to have considerable mobility and can easily be brought up to the end of the common duct. The anastomosis of the common duct, I believe, is easier; and there is less risk of stenosis, which to my mind is the chief cause of ascending cholangitis. In addition, it saves time by dispensing with intestinal closure. The pyloric end of the stomach can then be implanted into the jejunum 3–4 in. more distally.

Bath. C. Patrick Sames.

PSYCHOSES IN CHILDHOOD

Sir,—In your annotation of March 22 on a meeting at the Royal Society of Medicine at which I spoke, one sentence suggests that sphincter control and motor skill may be lost, coupling this together, and going on to say that the child becomes clumsy. This gives a distorted picture of what I said. The striking thing about these cases is the extent to which motor skill is retained. It would often appear that the *inability to do things* is due to a lack of interest, even perhaps to a lack of willingness to conform. My actual words were: "A child unable to feed himself or dress himself will balance on a narrow wall or twiddle a tin lid with fascinating dexterity" and this curious combination is one of the distinguishing features of these cases.

London, W.1. E. M. Creak.

ARTIFICIAL RESPIRATION

Sir,—Certainly Schafer's method is efficient, easily taught, and easily carried out; but there is little doubt that of the better-known methods of artificial respiration it produces the smallest respiratory excursion. This is inevitable as it is only a "push" method, and so, although expiration is full, inspiration is passive following the release of pressure, and thus essentially limited. A "push-pull" method, where both inspiration and expiration are actively assisted, is obviously more sound physiologically and likely to be more effective in practice. For these reasons, in America a modified form of the Holger-Nielsen method has been officially recommended for general adoption, and this method should be considered for official recommendation in this country.

To condemn this suggestion, as does Dr. Burnet (March 22), because first-aiders have been using Schafer's method efficiently for many years is not really progressive. *Further, the first-aider does not need to* be blinded with science in order to appreciate the superiority of the Holger-Nielsen method—one demonstration in which all members took the parts of both patient and operator convinced all the members of my division of the St. John Ambulance Brigade.

In addition to its physiological superiority the Holger-Nielsen method is easily taught, is very little more tiring to carry out than Schafer's method, and can be carried out by one operator. I feel certain that when it is more widely known its value will be generally appreciated; and, if only prejudices can be overcome, it will be universally adopted as the method of choice.

Harrow, Middlesex. A. R. H. Hicks.

ANÆSTHESIA FOR TUBERCULOUS PATIENTS

Sir,—I would agree with Dr. Mushin's plea (March 22) for a more rational approach to the problem of anæsthesia for patients who incidentally have pulmonary tuberculosis. Since lung resections have been introduced for the treatment of tuberculosis, necessitating the use of general anæsthesia, the traditional arguments for regional anæsthesia for thoracoplasties have been breached. It is this latter group, where control series between local and general anæsthetic techniques can be contrasted easily, that can produce the most relevant evidence.

I am at present compiling figures from my own experience for a more detailed examination with regard to thoracoplasties, but it is already evident that the particular dangers under general anæsthesia are: (1) new foci of disease arising by bronchogenic spread of sputum; and (2) "light-up" of quiescent foci, possibly by excessive stretching of lung tissue. It is essential, therefore, that the patient should be breathing quietly, and that bronchospasm and other respiratory disturbances should be avoided. The anæsthetic agent per se is irrelevant as long as it is capable of producing the above conditions.

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[1] *Brit. med. J.* 1935, i, 582.

For some time now we have taught in this hospital it general anæsthesia is not contra-indicated with idental pulmonary tuberculosis, except when frank itum is present or a fluid level is seen in a cavity, when patient should remain awake. Large artificial eumothoraces reducing vital capacity to the verge of spnœa are satisfactory under general anæsthesia so ig as respiration is assisted if it becomes depressed. My usual technique for obtaining the necessary smooth luction is thiopentone sodium mixed with 40–80 mg. gallamine triethiodide, continuing with cyclopropane d oxygen and further doses of a muscle relaxant if dominal relaxation is required. The use of thioatone alone as an induction agent in these particular es where irritable foci may be present in the lower piratory tract often leads to severe bronchospasm d coughing. The addition of gallamine should avert this. Endotracheal tubes should be avoided lest a damaged ynx become thereby infected.

t. Thomas's Hospital,
London, S.E.1. R. B. WRIGHT.

STANDARDISED SENNA

SIR,—As manufacturers of 'Senokot,' the granular oduct of senna pod referred to in your annotation of irch 29 (p. 655) as retaining the full laxative activity of ide senna, may we point out that the advantage of standardised preparation is not merely the avoidance overdosage and therefore of griping; it also enables e clinician to assess the actual or potential value of ina in a given condition.

Vestminster Laboratories Ltd.
London. E. W. GODDING.

THE UNESTABLISHED PRACTITIONER

SIR,—In the last issue of your journal Dr. Frank Gray fends the policy of the B.M.A. towards the unestabhed practitioner under three headings. I would rather ve crossed swords with him on the fundamental issue the unestablished doctor and the policy of the Unestabhed Practitioners Group. Perhaps Dr. Gray would tline his views on this policy?

At present I must confine myself to answering his triple fence:

1. Dr. Gray denies that the association has refused to pport any betterment of the unestablished doctor, or to onsor any plan to encourage partnership. His sole evidence the "charter for assistants which now appears in the sociation's handbook." This charter is a confirmation of e status of the assistant on a commercial basis with a fullme salaried service. Furthermore, the B.M.A. itself has fused to take any action against principals who refuse to plement the charter. When an assistant draws attention abuse of the charter by his principal, the Medical Practices' dvisory Bureau of the B.M.A. advises the assistant to ange his job! Surely Dr. Gray does not wish us to believe at this is the B.M.A.'s contribution to the problems of e unestablished after three years?

2. Dr. Gray claims that the Assistants and Young Practioners Subcommittee of the G.M.S.C. represents the unestabshed. That is for the profession to judge. May I draw ttention to the following facts: (*a*) Dr. Gray's subcommittee ontains six "established" members from the G.M.S.C., not our as he stated; (*b*) This subcommittee has never held a ingle meeting in any of the regions and has made no effort to scertain the views of the unestablished practitioner by any iethods; and (*c*) This subcommittee has not even in its title ecognised the word "unestablished" with its implications. n three years of existence it has never given any lead to he unestablished practitioner nor any assurance that his indamental problems are even realised! Since this subommittee is secretive both as to how it receives guidance rom the unestablished practitioners and as to its discussions r influence or conclusions, perhaps the views of one or two f its members may help the profession on this somewhat idden problem.

Finally, Dr. Gray admits that the Working Party does iot include an unestablished practitioner. Would the G.M.S.C. consider inviting one or more unestablished practitioners to give their views to the Working Party? Dr. Gray states "the views of the Assistants and Young Practitioners Subcommittee have been fully expressed to the Working Party." Will he at least assure the profession that these views have been expressed to the Working Party by one or more "assistants or young practitioners" and not by an established principal?

L. RUSSELL
Chairman, Unestablished
London, N.W.6. Practitioners Group.

SIR,—As one of the hopeful "unestablished," may I take up Dr. Gray's second point?

Last year the General Medical Services Committee of the B.M.A. wrote asking for postal votes to elect their "Assistant and Young Practitioners Subcommittee." They submitted a list of names quite unknown to me and, I expect, to many others, giving no details of their qualifications to be on such a committee, except that somebody had nominated them. Thus, although I would have wished to, it seemed irresponsible to vote for somebody about whom I knew nothing. This subcommittee was duly "elected." Surely Dr. Gray and his associates must realise that they can hardly describe this as a "democratically elected subcommittee!"

Since then I have not heard anything from this "fully representative subcommittee." They appear to have held no meetings to canvass the opinions of the members they claim to represent, yet they express *their* views to the Working Party.

Perhaps this subcommittee would call a meeting (or meetings) of the assistants and unestablished practitioners so as to allow a fresh election to be held, since until this is done they cannot reasonably claim to speak for these doctors—at least 10% of the general practitioners.

Teddington, Middlesex. JOHN FOLEY.

UNEMPLOYMENT AMONG DOCTORS

SIR,—Having long supported the principles of the National Health Service, in 1950 I returned to my native land, with wife and 2 sons, to enter general practice—only to be confronted by the unprecedented situation which amounts virtually to unemployment amongst doctors. Inasmuch as I had had no previous experience of general practice in the U.K., I was eventually able to secure employment for one year only through what must be a very wasteful form of subsidy, the trainee-assistant scheme.

The causes of this situation are not, I think, fairly attributable to the N.H.S. Act, to the ban on sale of practices, &c., but (*a*) to the large number of students qualified since 1939 (basically a desirable trend), (*b*) to the natural reluctance of older doctors to relinquish any of their practices to partners or successors in these times of inflation, and (*c*) to the difficulty of raising "development" capital—i.e., to start new practices. Banks are forbidden to advance such loans, and building societies are reluctant to consider a mortgage when a doctor is not succeeding to a list of patients and has no other source of income.

The Medical Practices Committee's report last November, and a second leader in the *Times* prompted by it, were astonishingly complacent on this subject. Both contended that the length of the list of "open" areas did not support the complaint that entry to general practice was difficult. But in suggesting that the young doctor take advantage of "the length of the list of open areas" they are suggesting that the way for him to enter general practice is by starting a new practice—i.e., by squatting. This probably is the most satisfactory way of entering general practice, but it requires more capital and more financial courage than the community is entitled to expect of its new doctors after a long academic and clinical training.

The present situation discourages mobility within the profession, whereby men with varied experience might bring new ideas to their freshly adopted branch of medicine. This lack of mobility, incidentally, may well be one of the chief factors hindering the progress of our industries and professions as compared with those of North America. It is especially hard for those of us who, after a period of war service and several years as registrars or in some specialty, attempt to enter general practice. During such a period most of us have accumulated family responsibilities and not much capital, which makes employment an urgent matter, but our experience is liable to be discounted as irrelevant to general practice. This I think is grossly unfair, since the experience of a specialty is often of great use to a general practitioner.

Where for humanitarian reasons we are committed to a policy of providing more doctors than the community would support on purely economic grounds, we must take special steps to place those doctors. In the new towns this is being done by setting aside a house for the doctor and advertising the new practice as an executive-council vacancy. Similar steps to create new practices should probably be taken in, say, all Schedule I areas.

Until some such scheme provides us with employment, Britain is likely to lose a substantial proportion of its ex-registrars, who will follow, or have preceded, me to Canada and other parts of the English-speaking world.

Approaching Nova Scotia. A. G. RICHARDS.

THE TREATMENT OF PEPTIC ULCER

SIR,—Mr. Richardson (March 29) states that an English version of Lenhartz which I quoted, was a travesty of the original régime. On this point perhaps your readers will judge. During the first five days, the English version supplied a total of 2325 calories,[1] against a total of 3069 in the original régime.[2]

Mr. Richardson still misses the salient point. Patients did not die from starvation, but from therapeutic dehydration during these critical early days when the feeds were so small that the fluid intake was automatically grossly restricted. Morphine certainly allayed thirst, but did not prevent death from dehydration. This cause of death was effectively eliminated by the policy of the liberal feeding of hæmatemesis patients introduced by Meulengracht, to whom all credit should be given.

Department of Gastro-Enterology,
Central Middlesex Hospital,
London, N.W.10. F. AVERY JONES.

CEPHARANTHIN AND TUBERCULOSIS

SIR,—We would like to add our mite to the growing weight of evidence against cepharanthin.[3] We obtained a small sample of this substance, and the following three experiments were made:

1. Cepharanthin was incorporated in Löwenstein-Jensen medium in amounts varying from 0·1 to 1·0 mg. per ml. No inhibitory effect was observed when these media were inoculated with various strains of *Mycobacterium tuberculosis var. hominis.*

2. 3 mg. cepharanthin was injected intraperitoneally twice a week into each of two guineapigs. After three injections these animals and two similar control animals were infected with a small standard dose of *Myco. tuberculosis* given intramuscularly. Two guineapigs continued to receive cepharanthin as before. No prophylactic effect was observed either in delay of onset of the local lesion or in generalisation of the infection. All guineapigs were killed after six weeks and presented a similar pathological picture.

3. Three groups (A, B, C), each of eight guineapigs, were infected with a small dose of *Myco. tuberculosis* intramuscularly. Guineapigs in group A were treated with cepharanthin 5 mg. daily intraperitoneally. Those in group B received 5 mg. twice a week. Group C were not treated. The experiment was continued until all guineapigs had died of generalis tuberculosis. The average survival-time was not significantl prolonged in either of the treated groups.

Uninfected guineapigs were found to tolerate 5 m cepharanthin twice a week. Two which were given 5 m daily developed plastic peritonitis, from which one of the died.

These observations, though incomplete, may be of som interest. Taken together with the evidence alread published, we did not feel that these results justifie us in proceeding any further with tests of cepharanthi

W. P. STAMM
K. R. DUMBELL.

HERNIATION OF THE NUCLEUS PULPOSUS

SIR,—Mr. Hogg's letter (March 22) refers to M Charnley's hypothesis. While I do not wish to belitt Mr. Charnley's excellent article (Jan. 19), I would poi out that the identical hypothesis was put forward by m in a Hunterian lecture on March 29, 1951[1]; whil the hydrophilic properties of the nucleus pulposus we demonstrated by Gocke in 1932.[2]

I hope shortly to publish further clinical and expe mental evidence in support of this hypothesis.

Bradford. A. NAYLOR.

THE ADJUDICATION

SIR,—Following the award of Mr. Justice Danckwe on March 25 there appeared in the *Times* the followi words:

"If the 'central pool' system is to be retained . . . t principles on which it is based require reconsideration. . Present methods . . . *put a premium on the* quantity patients to the detriment of the quality of service; they te to set doctors in competition for patients. . . . The nati will not grudge the doctor his new fees, but it has every reas for expecting that he should be paid in ways which encoura good work—and economy in prescribing."

If these recommendations are to be given effect, m I once again through the courtesy of your columns bri forward proposals for distribution of the central pool a manner which would give effect to them?

1. Basically an expenses allowance sufficient to cover doctor's overhead expenses allowable for income-tax purpos

2. Yearly increments for length of service for the first t years, after which it would remain stationary.

3. Specialist pay for holders of the F.R.C.S., M.R.C.P., &c., those who had passed an approved course of *training* general practice.

4. *Special locality allowance to be given in difficult are* which might include spa and health resorts where a lar number of elderly people congregate (Spens report, para. 1

5. Mileage allowance as at present.

6. A small capitation fee for each patient to represent on a personal factor for responsibility assumed up to 25 patients only.

By these means the emphasis and encouragement cou be on quality rather than quantity; a doctor once aga becoming a craftsman instead of a contractor buildi up a large business connection.

Worthing. HAROLD LEESON.

INFORMATION ON EUTHANASIA

Dr. Maurice L. Millard writes as follows:

My father, the late Dr. C. Killick Millard, was in 19 associated with the late Lord Moynihan and the late C. Bond, F.R.C.S., in the founding of the Voluntary Euthanas Legalisation Society, of which he was hon. secretary unt his death on March 7. He conducted the affairs of th society with great energy and enthusiasm from his ow residence at Leicester. He has left a large stock of pamphlet &c., bearing on the subject of voluntary euthanasia, and any medical man or woman is interested, his executo (c/o, The Gilroes, Groby Road, Leicester) will be glad t forward literature to them.

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[1] Searle, F. W. Pharmacopœia of St. Bartholomew's Hospital. Shrewsbury, 1936.

[2] Spriggs, E. I. *Quart. J. Med.* 1911, 4, 399.

[3] See annotation, *Lancet*, 1951, ii, 437.

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[1] *Ann. R. Coll. Surg.* 1951, 9, 158.

[2] *Arch. Orthop. Mech-Ther.* 1932, 31, 43

Parliament

Administration of the National Health Service

IN the House of Lords on March 26, Viscount BUCKMASTER pointed out that the cost of the service had now ched the £400 million mark. Every ceiling which ery Chancellor of the Exchequer had imposed was mediately penetrated, and the cost of the service med to have no upward limit. If we were to count the st, as we must, then he urged we must not count the tes. We must make economies which would leave quality of the service undiminished. It should be ssible. Last year, for instance, every man, woman, d child in this country had four prescriptions. He o thought the intervention of regional boards between hospitals and the Minister must cause waste and lay. Again, some of the regional boards were perhaps large. He felt the method of selecting members ould be on a more democratic basis, and he would e to see a delegation of power from the centre to the spital management committees.

Lord Buckmaster welcomed the decision to increase e remuneration of general practitioners, but he did not lieve that in itself it guaranteed any cure of existing ils. Most of the flaws in the scheme derived from the akness of the general practitioner's position. The most must be done to improve his status and standing, d to encourage young men of the best type to enter neral practice. Today the general practitioner felt t only that he was excluded from the hospital field, it also that the cottage hospital was too often becoming specialist unit and closing its doors to him. The omised health centres had proved to be chimeras and doubted whether they would ever exist. The doctor id to be given a feeling of confidence in the future of neral practice, not purely as a means of earning oney, but as a field in which he could exercise the art healing.

Lord SHEPHERD pointed out that the organisation of ie N.H.S. was largely determined by the fact that arliament was responsible for it. Parliament, in turn, aced these responsibilities on the Minister of Health. he Minister could have said the most efficient way to in the service would be through a professional staff— s in the Army, Navy, and Air Force. But the Minister id Government of the day believed that as the service ad to deal with the community as a whole it would be etter to use the voluntary help of local men and women. gain the Minister could have secured contact between imself and the 400 hospital areas through a professional aff. Instead he chose to set up the regional hospital oards. Thus the whole organisation of the N.H.S. was ased on voluntary service.

Turning to finance, Lord Shepherd said he could not nderstand the suggestion that, with income-tax at s. 6*d*. in the pound, we should give block grants to ospitals and not persist in asking too many questions. f we had to pay due regard to economy we must maintain he Parliamentary system and ask hospital authorities o submit estimates. A H.M.C. given a block grant would ave to do its best on the money provided. and he looked pon the submission of estimates by management committees and regional boards, as one of their rights, to nake their local requirements clear to the Government. eplying to the criticism that estimates encouraged .M.C.s to spend any surplus balance, he said he thought he present itemised system of accounts gave little pportunity for waste of this kind.

MEDICAL PROBLEMS AND POLITICAL ISSUES

Lord MORAN earnestly asked the House not to allow olitics to enter into the health of the people. To say hat the charges on prescriptions and dental treatment lemolished the structure of the health service was, he uggested, politics. No doctor would believe such riticism. Surely the foundations of the service were not so shaky as that. We had been building scaffolding or many years; presently there would be a building. For any section of the community who had difficulty in entering it because of these charges surely we could devise a free pass.

Lord Moran thought there was general agreement that a good deal of discontent existed among the practitioners. Some claimed that this unrest was financial in origin. If so, then Mr. Justice Danckwerts's judgment would perhaps reconcile them to the service. But he felt that a more deep-rooted cause was the insidious decline in the status of the general practitioner over a number of years. This began when men and women, vaguely conscious of the technical advances in medicine and surgery, decided that when they were seriously ill they were safer in hospitals under specialists than in their own homes under their own practitioners. How common the use of hospitals had become was shown by the fact that 1 in 15 of the population was an inpatient every year, and 1 in 7 an outpatient. The general practitioner could put up no kind of resistance to this tendency, because, owing to the scarcity of nurses and domestic staff, it was difficult or even impossible to treat serious illness in the patient's own home. But when he saw one of his patients entering hospital in a medical emergency it was a blow to his pride of craftsmanship. The decline in his status was not the result of the N.H.S., but of the conditions of his life before. Another blow did fall on the practitioners as a result of the passing of the N.H.S. Act. The best of them had made modest excursions into the specialist's field. The Act took all that from them. Lord Moran did not say this was wrong, because consultants or specialists should obviously be *trained* as such, but the fact remained that the practitioner's life had been denuded of much that made it absorbing in the past.

The clock could not be put back. We should not be able to persuade patients to be treated at home. The only remedy was to allow the practitioner to follow his patient into the hospital. Lord Moran thought this more important than any reform in medical administration which had occurred in his lifetime. But it was not going to be easy and would meet with much opposition. The hospitals were largely staffed by specialists—there were 500,000 beds in the country of which only 6449 were in general-practitioner hospitals. Naturally the specialists were proud of their institutions and jealous of their good name. They would resist the dilution of labour as every other section of the community had done. He also feared that the general practitioner might be tepid in pressing for admission to the hospitals. If he was given access to diagnostic aids, and if the number of G.P. hospitals were increased, the G.P. might well be content. But Lord Moran believed that a G.P. hospital, though it brought contentment to the practitioner by providing good nursing and diagnostic aids, was a place where he tended to work by himself generally on knowledge acquired perhaps 20 years ago. To placate the G.P. we must not set up two standards of hospital treatment. The specialist in his hospital worked under ideal scientific conditions and in a critical atmosphere. It was important, Lord Moran held, that G.P.s should be drawn into this scientific atmosphere. It was surely not right that 5000 consultants should work under ideal conditions while 20,000 practitioners were working under scientifically unsound conditions. Lord Moran hoped that the difficulties of getting the practitioners into the hospitals would be boldly faced.

It was not yet known how the judgment of Mr. Justice Danckwerts would work out, but there was a feeling that the average general practitioner would earn more in the year than the average consultant. If that turned out to be so, Lord Moran said, it would be hard to persuade the student of promise to obtain the higher qualifications required by a consultant. It was important to preserve the financial balance between the two branches of the profession. The practitioners had now been awarded 100% betterment, while up to date the consultants had been given 20%. He believed that the consultants would act with responsibility and not pitch their claims too high; but the position had to be set right. If not, eventually the consultants would go to arbitration, and arbitration, Lord Moran suggested, was not necessarily economical.

Everything depended on how the Danckwerts award was distributed. Readjustments in the capitation fees would make it possible for young men to enter practice and for older men to have more time to do their work properly. If a doctor with 4000 patients on his list were paid generously for the first thousand and not at all generously for the last, much good might come of it. Again, looking after old people and children was more arduous than attending an adult, and Lord Moran suggested that two aged people might count for three on the doctor's list. Lord Moran believed that on the whole there was surprisingly little waste in hospitals. But he agreed economy was vital, for expensive new techniques and drugs would have to be incorporated in the service. He realised that "hotel charges" were a political issue, but speaking as an innocent doctor, rather than lower the standards of the hospitals, close beds, or cut schools, he would charge people 3s. a day or £1 a week for food, making exemptions where necessary. The general Exchequer would benefit by £10 million a year.

Some £50 million a year was spent on drugs, and here Lord Moran suggested economy was possible. The shilling charge on prescriptions had the disadvantage that it was a charge on a sick man. In Denmark drugs were divided into three categories: the lifesaving essential drugs which were given free; the desirable but not essential drugs for which the public paid 40% of the cost; and the placebos for which the public paid 100%. This plan had been a success in Denmark, and in Australia it had been in operation for 18 months. Lord Moran thought the debate had been useful in unravelling medical problems from political issues. More important, it had confronted the public with the need to decide whether they would have a free but inadequate service or a really good service to which they would have to make a contribution.

Lord WEBB-JOHNSON pointed out that it was essential to remember that the cost of the health service was linked with the country's financial position, and the service had a place in the fight for national solvency. He admired what the service had accomplished, but he believed some modifications were necessary. The dangers of remote control, for instance, had not been avoided. The hospital boards had been burdened with too much concern about details, whereas they were established for policy-planning and coördination. If individual hospitals had more discretion they might secure more efficiency and in the end effect more saving. There was considerable disquiet throughout the country because the H.M.C.s had no direct responsibility to the communities which the hospitals served. One means of easing financial strain would be to increase pay-bed accommodation on reasonable terms. He also supported the idea of a hotel charge. Medical investigation and treatment today were enormously more costly than formerly. The country could not have a good health service unless the general practitioner was given a chance to do his work properly; and it was only the Ministry of Health backed by Parliament that could provide him with adequate facilities.

The Earl of ONSLOW, replying for the Government, said the Danckwerts award was a complicated matter and they would wish to study it before expressing any considered view upon it. Remuneration and doctors' lists were still under consideration, and it would be improper to discuss them. The fact that doctors' lists were considerably inflated arose from the difficulty of keeping the register up to date. Neither the present Government nor their predecessor were satisfied with the working of the 1946 Act. He thought they would agree that it required amendment from time to time. There was a Working Party, consisting of members of the medical profession and of the health departments, considering an equitable distribution of the central pool. A committee of the Central Health Services Council, under the chairmanship of Sir Henry Cohen, was considering the broader aspects of the organisation of general practice. Overprescribing was much in the Minister's mind, and a booklet, *Prescribers' Notes*, was being sent round to doctors. The introduction of hotel charges for hospital patients was not in the mind of Her Majesty's Government at the moment.

The Charges

On March 27 in the House of Commons, Mr. H. F. C CROOKSHANK moved the second reading of the Nationa Health Service Bill, which enables the Government t make the charges on the National Health Service outline by the Chancellor in January. Not unexpectedly a goo deal of the seven-hour debate was spent discussing whic party was actually responsible for the introduction o the charges: "When is a charge not a charge?" aske Mr. Crookshank. "When proposed by the right hon member for Ebbw Vale." But apart from these historica excursion [illegible] ure of the economi backgrou [illegible] ges were being impose and the [illegible] that may be met i implementing them.

In his opening speech, Mr. Crookshank admitted tha he expected the charges to be attacked by the Opposition but people who were not engaged in politics might wel be surprised if, at a time of general public saving, th National Health Service should automatically be pu out of bounds. Nor was this Bill an attempt at retrench ment at all costs. The Government believed that beside restraining expenditure it might by a shift of emphasi alter the course of the service in the right direction First of all, he said, he would like to stress that 90% of the service was paid for out of taxation. Of the weekly 113*d.* on a worker's card the 10*d.* which went to the N.H.S was a small contribution and neither an insuranc premium nor a payment for service rendered. To impos a charge was therefore not breaking faith with anyone To keep the service within the £400 million ceiling th last Government had put a charge on dentures an spectacles. Costs were still rising, and he and his colleagues were working to exactly the same ceiling and doing exactly the same thing—putting on charges.

Summarising the clauses of the Bill Mr. Crookshank explained that the late Government, though they had never used it, had taken power in the Act of 1949 to make a charge for medicines and appliances prescribed by general practitioners. This Bill extended this power to outpatients at hospitals. Inpatients would continue to get their medicines and appliances free. Only a small range of appliances would be affected: surgical boots, abdominal supports, elastic hosiery, and wigs. The charges for these were expected to bring in about £250,000. There would be no charge for appliances to school-children, to people in receipt of National Assistance or their dependants, or to war pensioners in respect of "accepted" disability. Cases of hardship would be dealt with in the same way as was proposed in the 1951 Act.

SOME NEW ISSUES

Originally two exemptions to the dental charges had been suggested—school-children and expectant mothers. In view of the argument as to whether the right exemption age had been chosen the Government had now decided to raise it from school-leaving age to 21. This would reduce by about £1 million the £7½ million they expected to save from these charges. They hoped these charges would encourage more dentists to join the school dental service, possibly on a part-time basis. To meet the objection that the £1 charge would reduce real conservation work for adults the Government had decided that the charge should begin only after the mouth had been examined. Clinical examination would be free.

As regards the Danckwerts award he believed that assuming the £30 million *back-log* was taken out of the account the £10 million increase for next year could be met without greatly exceeding the ceiling. It was not the intention of the Government as a result of the Danckwerts award to increase any of the charges in this Bill. If as a result of the award the £400 million ceiling was surpassed in 1952–53 that was a situation we should have to accept. The ceiling would have to go up because it was a situation which no-one could fully foresee.

EXTRAVAGANT PRESCRIBING

Dr. EDITH SUMMERSKILL opposed the Bill because it erected a financial barrier between the doctor and the poorest in the community. There was no comparison between a once-for-all charge borne in the main by healthy people, such as the charges on dentures and spectacles, and this Bill. Every old person in the lowest income group, the small pensioners, the widows, the blind, the orphans, and the chronic sick would suffer hardship. No doctor, however warm-hearted, could give a prescription for a chronic patient for three months and then wash his hands of the treatment.

Did the Minister realise where the most flagrant abuse of the scheme existed, she asked. It was an abuse in the main by the better-off section of the community at the expense of the worse-off. She did not deny that the drug bill was too high—one-eighth of the total expenditure. But it was never out of control before 1946 when only the lowest-paid workers were entitled to treatment. It was out of control today because high-powered salesmen on behalf of the drug manufacturers are persuading doctors to prescribe expensive proprietary drugs for their more well-to-do patients. Doctors were departing from the *National Formulary* and prescribing unnecessary and expensive drugs. The approximate proportion of proprietary prescriptions in the N.H.I. scheme before the war was 3%. It rose to 7% by 1947, to 12% in 1948. By the end of 1949 it was 21%, and today it was over 30%. Who were consuming these expensive drugs? The average cost for a prescription for the whole country was 3*s.* 8*d.* But there were astonishing local variations. Pharmacists practising in seven districts of Greater London lately compared their cost of prescriptions. In one suburban area of high rateable value the cost was as high as 7*s.* 6*d.*; in a favourite residential area on the borders of Middlesex it was 6*s.*; in a large and varied urban district it ranged from 2*s.* 10*d.* to 4*s.*; while in a crowded industrial area it was as low as 2*s.* 3*d.* Clearly the source of the Minister's saving should be not the pocket of the sick poor but the millions spent on expensive drugs for better-off people. Dr. Summerskill advised the Minister to revise the *National Formulary* more often and to instruct chemists not to dispense proprietary drugs unless the doctor indicated that there was no equivalent in the *N.F.*

THE SACRED CEILING

Mr. ANEURIN BEVAN believed that the Danckwerts award had shocked our majority of people. Something had gone wrong with our sense of values in this country when we could confer £40 million upon one branch of the medical profession and at the same time propose charges on old-age pensioners. He had resisted a proposal to put compulsory arbitration into the National Health Service scheme because he thought it would destroy the Whitley council machinery, ruin the relationship between the Government and the medical profession, and put the budget outside the House. The sacred ceiling they had been told had been busted, and it had not been done by the House of Commons but by someone outside. He believed that the G.P.s were entitled to an advance, and if any funds were available for the improvement of the N.H.S. they had the first claim. But there was all the difference in the world between providing a reasonable increase and adding this enormous sum which would be an irritant in every industrial negotiation in Great Britain. The gap between professional awards and manual workers' standards was getting too wide. Large numbers of professional workers were now educated at the expense of the State and no longer had to give up earning money to equip themselves.

In Mr. Bevan's view if money had to be saved on the N.H.S. the logical way was to put a certain service, such as dental treatment or drugs, outside the scheme. But to have a service half in and half out made all kinds of administrative difficulties. After one full year's experience he had been able to give the Chancellor an estimate for the whole of the next year's expenditure. This proved, Mr. Bevan declared, that the British people had shown a predictable pattern of behaviour. Yet instead of people being proud of it and saying, " here are fine people who are beginning intelligently to use this free service," the scheme was abused. In 1950–51 the expenditure on the dental service and ophthalmic service was falling; the same was true of artificial limbs. We had worked off the arrears of neglect. It was not true of the pharmaceutical side. Why? In the first place, he believed, because the medical profession was ill-disciplined. But another reason was the increase in the use of the new expensive remedies.

Mr. IAIN MACLEOD pointed out that the ceiling of £400 million was an irrational one and suggested that between now and the next budget we should study the proportions which health ought to bear to the whole of our national expenditure. The Danckwerts award delighted him. Hitherto we had had an unbalanced scheme in which we paid more in gross income to 10,000 dentists than to 20,000 general practitioners, in which the expenditure on drugs was £11 million more than the amount paid to the general practitioners. Now we had a chance to get the scheme back into balance.

He agreed that charges had a deterrent effect. The charge on dentures had probably had a deterrent effect of about 50%. But a deterrent charge was an advantage if a switch of resources followed. He believed that particularly with poor people health expenditure was a marginal expenditure and was one of the first things that went. The deterrent charges might therefore well have a greater effect than was expected. If so he hoped the Government would be able to reduce the charges.

INCENTIVES AND DETERRENTS

Mr. HECTOR MCNEIL was anxious that the Working Party charged with the arrangements for the distribution of the Danckwerts award should see that large lists would be discouraged and benefits offered to the family doctor who really is doing his job with a list of under 3000. The present fee of £300 offered to a young doctor was ridiculous. Mr. McNeil suggested £800 to £1000 a year as a more appropriate sum.

Mr. HUGH LINSTEAD believed that most of the increase in the drug bill was due to expensive new remedies rather than to proprietary drugs. Only an efficient pricing system could pick out the doctors who were over-prescribing. Mr. JOHN BAIRD held that the school dental service was always inefficient and second-rate. To argue that we are destroying it was ridiculous. Though there had been some reduction in the school dental service, many more children were being cared for in private practice and getting better treatment than before. Dr. BARNETT STROSS agreed that the charges had reduced the demand, but he was not so sure that they had prevented abuses. Were they not only stifling the demand among the people who can least afford it?

Mr. H. L. MARQUAND thought the most evil feature of the Bill was that it sought to impose charges in perpetuity. It did not recommend the charges, as he did a year ago, as a distasteful necessity but as something good in themselves. These charges fell on the sick and discouraged people from taking care of their teeth. Raising the age of exemption and freeing examinations from the charges were, in his view, improvements in a bad measure. But the charges still remained objectionable, for they were charges on treatment. Furthermore the charge for prescriptions was a breach of contract to all who had contributed to National Health Insurance at any time between 1911 and 1948. He particularly regretted that there was no exemption from the prescription charge for children. The greatest benefit of the N.H.S. had been that it gave the poor for the first time the opportunity to secure a true family-doctor service.

Commander T. D. GALBRAITH, joint under-secretary of State for Scotland, pointed out that it was the late Government which had placed a ceiling on the expenditure of the health service. Yet when the present Government took steps to keep within the ceiling they made violent protests. He had heard denunciations of the Government's proposals during the debate, but he had heard few suggestions as to what might be substituted for them. The main objection to the prescription charge was that people who suffer from chronic maladies would be hard hit. But there was nothing to prevent the doctor, if he saw fit, from prescribing sufficient drugs to last weeks or even months. It had been suggested that, instead of refunds, arrangements should be made for exemptions from the charges. But no exemption scheme could be administered unless doctors were saddled with an unfair responsibility for identifying which patient should be exempted. Instead the Government had made refunds as easy as possible for those whose need was greatest. The modest charges proposed in the Bill were, he ended, a more sensible way of meeting the critical situation which now faced us than risking the collapse of more vital parts of the health service. These charges were to be preferred to inroads on the essential features of the scheme—the family doctor and the hospital services. If these could be preserved for the use of the people without financial impediment, the high ideal of the National Health Service had not been betrayed. The second reading was carried by 304 votes to 279.

DANCKWERTS AGAIN

In the debate on the Money Resolution which followed, Mr. BEVAN pointed out that the terms of reference of the adjudication bound the Government and the General Medical Services Committee to accept the award " subject to the overriding authority of Parliament." The Minister had said the ceiling must be exceeded to meet the award, and Mr. Bevan asked if there could be some early opportunity of discussing " this most significant decision before an outside body can appropriate large sums of money from helpless Parliaments." The point was ruled out of order on the Money Resolution, but Mr. CROOKSHANK agreed that on a proper occasion it should be discussed. Mr. BEVAN then asked for an assurance that no physical steps should be taken by the Government to implement the adjudication until the House had considered the matter. But no further answer was given.

Tuberculosis Among Bradford Foreign Workers

In the House of Commons on March 17, Mr. W. J. TAYLOR drew attention to the high incidence of tuberculosis among European volunteer workers (E.V.W.S) in Bradford. There were some 8000 of these workers in the city and suburbs and they had done a good job of work in this country and had helped us along the way to recovery. Some of them found themselves here at the end of the war as a result of having served in the Polish army. Others, who came in under the Ministry of Labour European Volunteer Workers' scheme were medically examined before being accepted for employment here. Some of them came by private arrangement with prospective employers, and for their fitness the onus rested on the employer. Over and above all this, all foreigners coming to this country were liable, under the Aliens Act, 1920, to medical examination by the immigration authorities at the ports. It was this examination, Mr. Taylor declared, that he would like to see tightened, for many people seem to have been admitted to this country suffering from active tuberculosis. Mr. GEORGE CRADDOCK was disturbed that of a whole family only the person who was to be employed was examined before they entered this country.

Miss PATRICIA HORNSBY-SMITH, parliamentary secretary to the Ministry of Health, said that until 1948 there was no check on the health of persons coming into this country, and owing to the privations suffered by many of these workers there was a higher than average incidence of tuberculosis among them; but since then, as a result of action taken in association with the Ministry of Health, the incidence has been reduced. In Bradford 50 E.V.W.S were suffering from tuberculosis, 41 of whom came here before 1948. Only 9 had come after the 1948 check. All workers were now checked in camps in Europe before being allowed to come here. The Ministry had come to the conclusion that it was impossible to examine at the port every foreigner who comes to take up employment in this country, because facilities were inadequate. Nor was it practical to make incoming aliens produce evidence at the port that they were free from tuberculosis. Such a proposal would involve medical and administrative organisation out of all proportion to the risk involved. In Bradford deaths from respiratory tuberculosis had fallen from 0·47 per 1000 in 1946 to 0·35 per 1000 in 1950. That city's record compared favourably with that for the rest of the country.

QUESTION TIME

Alastrim in Rochdale

Mr. C. R. HOBSON asked the Minister of Health what advice the medical officers of his department, who recently visited Rochdale and Milnrow, gave to the local medical officer of health on the measures to be taken to deal with the epidemic diagnosed as variola minor; and, in view of the fact that this disease was similar to the one described in his department's review of the Vaccination Acts, 1867 to 1907, as a disease which, if taken by itself, had no more formidable consequence than chickenpox or varicella, if he would amend his regulations so as to remove variola minor from the list of notifiable diseases.—Mr. H. F. C. CROOKSHANK replied: Medical officers of my department have been to the Rochdale area to study the outbreak of smallpox of the type known as variola minor, and to place their knowledge at the disposal of the local medical officers of health, who have the responsibility for taking such measures as they judge necessary to check the outbreak. As I am advised, it would be dangerous to the public health to do away with notification of this form of smallpox; to do so would also be incompatible with our international obligations.

Medical Superintendents of Scottish Hospitals

Mr. WALTER ELLIOT asked the Secretary of State for Scotland if he would give an assurance that the traditional Scottish system of hospital administration, under which the chief executive officer in a hospital was a medically qualified person, would continue under the National Health Service: and whether he was satisfied that the terms and conditions of service presently applicable to medical superintendents were such as to ensure that a sufficient number of doctors of suitable quality and qualifications would apply for these appointments in the future.—Commander T. D. GALBRAITH replied: There is no suggestion of altering the present Scottish practice, which is to employ medical superintendents for appropriate administrative duties in hospitals, rather than entrust such work to non-medical officers with the assistance of medical staff committees. Negotiations about the remuneration of these medical superintendents are in progress through the Whitley Council machinery.

Tuberculosis in Glasgow

Mr. WILLIAM REID asked the Secretary of State for Scotland the total number of deaths in Glasgow from pulmonary tuberculosis in 1949, 1950, and 1951, respectively.—Commander GALBRAITH replied: There were 1098 deaths in 1949 and 918 deaths in 1950. The provisional figure for 1951 is 650.

In answer to a further question Commander GALBRAITH stated that at the end of February there were 549 Glasgow patients awaiting hospital treatment for respiratory tuberculosis, of whom 122 had been on the waiting-list for more than 12 months.

Tuberculosis Treatment in Switzerland

Mrs. JEAN MANN asked the Secretary of State for Scotland if he would report on the Scottish scheme for tubercular patients to go to Switzerland; and whether this would be continued, extended, or abandoned.—Mr. JAMES STUART replied: I am glad to say that the scheme is going well. There are now 167 patients in Switzerland and others will be sent as and when these patients complete their treatment. The first main party came home last week and have already been replaced. The scheme is being continued and by early summer we hope to have a full complement of 150.

Hospital Administration in Scotland

In answer to a question Mr. STUART stated that the administration expenditure of regional hospital boards in Scotland for the year 1950–51 was £258,616.

Collection of Prescription Charge

Mr. GEOFFREY DE FREITAS asked the Minister of Health what representations he had received from local medical committees in Lincolnshire to the effect that dispensing rural practitioners should not be made responsible for the collection of 1*s*. for medicines dispensed.—Miss PATRICIA HORNSBY-SMITH replied: One of these committees has represented that dispensing doctors should not be responsible for the collection of the charge. The Minister is about to discuss these difficulties with the British Medical Association.

Medicine and the Law

Hospitals and Negligence

THE recent decision of the Court of Appeal in Clarke v. Worboys and others, reported in *The Times* (March 18), is important. Mrs. Clarke entered the Luton and Dunstable Hospital for an operation for carcinoma of the breast. This was successfully performed by the surgeon; but, in the application of electric coagulation, an electrode, placed under the right buttock, severely burned the patient and permanently injured the muscles.

Sued for damages, the hospital denied negligence. The plaintiff alleged that there must have been some want of care in the positioning or preparation of the pad; it was not sufficiently wet or a wrong solution was used. Mr. Justice McNair dismissed the claim; he seems to have thought that the injury might be due to a concatenation of factors, possibly including personal idiosyncrasy; at any rate he held that no negligence on the part of the hospital staff had been established. He added that, if the defendants had been found liable, he would have assessed the damages at £3000 for Mrs. Clarke and £1527 10*s*. for her husband (including £700 for the loss of his wife's services).

The Court of Appeal took the opposite view. They said that Mr. and Mrs. Clarke established a case to which no answer was given. Lord Justice Singleton observed that there was no negligence whatever on the part of the surgeon: the placing of the pad on the buttock was very common; there was evidence that, if the apparatus was properly applied, burning was unknown. Lord Justice Birkett, who seemed to infer that the preparation of the pad must have been faulty, said the court must decide in accordance with the preponderance of probabilities; this was overwhelming on the side of the plaintiffs. Judgment has therefore been entered for Mr. and Mrs. Clarke for the sums named, and leave to appeal to the House of Lords has been refused. In effect the Court of Appeal say that the burning of the patient is one of those things which simply ought not to have happened.

Normally a plaintiff who seeks damages for negligence must specify the negligence and must even state what precautions the defendant should have adopted. Exceptionally there are situations where the facts suffice to create the presumption of negligence, so that the burden is on the defendant to dislodge it. Thus, if a barrel be dropped out of a warehouse on an upper floor so that it injures a pedestrian in the street below (Byrne *v.* Boadle, 1863), or if six bags of sugar are allowed to fall on a customs officer at the docks (Scott *v.* London, &c., Dock, 1865), the law has declared that there is a presumption of negligence. So also if two trains collide on the same railway line. The facts speak for themselves; *res ipsa loquitur*. These things ought not to happen. On the other hand, it seems, there is no such presumption in cases of traffic accidents on the highway. Cases have arisen over defective machinery, but no case seems to furnish a precedent quite like that of Mrs. Clarke. Though she and her husband presumably consented to the operation, the defendant hospital was employing means which were potentially dangerous. Altogether it is a pity that no further appeal is permitted. One of the ablest of Her Majesty's judges placed the burden of proof upon the plaintiff; the Court of Appeal unanimously placed it on the defendants.

A Nurse's Occupational Risk

Next day the courts were deciding, in Michie *v.* Shenley and Napsbury Hospital Management Committee, another claim for negligence (*Times*, March 19). A male nurse on sole night duty was attacked and injured by a patient suffering from epilepsy. He alleged that the hospital had been negligent in not having warned him of the presence in the ward of a patient liable to become violent, and in having transferred the patient to a ward mainly occupied by patients of a non-violent disposition where a large measure of freedom was permitted. Apparently the patient became restless and began to interfere with other patients. The nurse telephoned, and a member of the staff came and administered a sedative. The patient went back to bed quietly, but presently jumped out and rushed to the door of the ward; finding it locked, he smashed its glass panels. The plaintiff pluckily tried to restrain him, but was struck in the face, knocked down, and injured.

Mr. Justice Barry held that no negligence or breach of duty had been proved. A mental nurse, he said, chooses his occupation with the knowledge that it is exposed to certain hazards, including the unpredictable conduct of mental patients, epileptics, and others; to make the care of such patients one's career involves expectation of assault and violence. The clinical reports and the medical evidence showed that it was perfectly proper to transfer this particular patient to the ward where the incident occurred. Neither the doctors nor the hospital staff had any reason to think there was more than a remote risk of his being violent. Actually the plaintiff had a clear warning of the violence; he could have obtained assistance before approaching the patient. He had been commendably courageous in tackling him single-handed, but the fact that he showed courage did not entitle him to blame the hospital for the consequences.

So the Shenley and Napsbury Hospital Management Committee succeeds where the Luton Hospital failed; the facts set up no presumption in the plaintiff's favour; he had to establish negligence and he did not do so.

Hypnotism on the Stage

Stage hypnotists, like stage conjurors, invite members of the audience to step up and take part in the performance. In the Brighton Hippodrome case (Rains-Bath *v.* Slater) the jury found that the invitation had a harmful result. The finding is timely for the promoters of the Hypnotism Bill who seek "to make illegal the demonstration of hypnotic phenomena for purposes of public entertainment."

As Mr. Justice Croom-Johnson was careful to tell the jury, hypnotism is lawful in the present state of the law. Nor, as he further pointed out, had the defendant, Mr. Slater, been attacked as a charlatan or humbug. The newspaper reports, it is true, have told us that at one time he used the title of "Dr." Slater on the faith of honorary degrees in science and philosophy which apparently arrived by post from a university in California. But he discarded the title as soon as he realised that it was bogus. He claimed to have hypnotised 25,000 persons, to have taught his technique to 3000 American doctors, and to have worked in the war as assistant to a neurophysicist at an Army clinic. Why then should he have been adjudged to have injured Miss Rains-Bath, the young lady who, having already seen his performance, volunteered for personal experiment? Her legal advisers stated her claim in three ways. She sued for breach of contract, presumably on the ground that Mr. Slater had undertaken to do her no harm; this part of the claim was not pursued. Secondly she sued for an assault; at one point Mr. Slater had caught her by the neck in reasserting his control; it was hardly more than a technical assault; the jury gave her a mere £25 for it. Thirdly, and most seriously, she alleged negligence. The defendant, she complained, had instilled into her mind depressing suggestions, causing her, amongst other things, to weep and to call out for her mother; and he had not, before bringing her out of her trance, implanted any reassuring belief that everything was really well and that she had no cause to be frightened. Mr. Slater did not deny that the girl had suffered depression and illness in the months following her experience on the Hippodrome stage; but he insisted that he himself was not the sole cause of her condition. The issue, of course was for the jury. The learned judge told them not to award damages unless the negligence was proved beyond a shadow of doubt. They gave her on this issue a verdict of £1000. Happily she is now, it seems, completely restored to health, having had a gentler and less abrupt hypnotic treatment during some six months from a registered medical practitioner.

The Hypnotism Bill, introduced into the House of Commons by one such practitioner and backed by four others, has been lucky in its opportunity of success in a Parliament wherein, as always nowadays, the Government monopolises the available time at the expense of the private member. The definition in the Bill is as follows:

> "Hypnotism" includes hypnotism, mesmerism and any similar act or process which produces or is intended to produce in any person any form of induced sleep or trance in which the susceptibility of the mind of that person to suggestion or direction is increased or intended to be increased but does not include hypnotism, mesmerism or any such simliar act or process which is self-induced.

The Bill forbids stage hypnotism "on any living person" at any entertainment to which the public are admitted. It contains a suitable saving clause for hypnotism "for scientific or research purposes or for the treatment of mental or physical disease."

The lay public will probably be curious to know how far such treatment is employed by orthodox practitioners, and how much good or harm it can do. When Mesmer's demonstrations attracted attention in the 18th century, the French government directed an official inquiry at which no less a person than Benjamin Franklin assisted. The recent litigation at Lewes assizes is less adequate than a Royal Commission as a fact-finding investigation, but the evidence and the verdict will not escape the attention of our legislators.

Appointments

ANNELS, E. H., M.B. Lpool, D.P.H.: deputy M.O.H. and deputy school M.O., Rotherham.

CHRISTIE, A. M., M.B. Edin.: appointed factory doctor, Gatehouse district, Kirkcudbright.

FERGUSON, HAROLD, M.B. Edin., D.M.R.D.: senior registrar in radiology, North Gloucestershire clinical area.

HART, C. B. L., M.R.C.S.: asst. M.O.H. and asst. school M.O., Rotherham.

MONKS, P. J. W., M.B. Lond., F.R.C.S.: surgical registrar, Bristol clinical area.

OAKENFULL, B. G. P., M.R.C.S., D.A.: part-time consultant anæsthetist, Scunthorpe and District War Memorial Hospital and County Hospital, Lincoln.

TRAVERS, ELIZABETH, M.A. Vassar, M.B. Manc., PH.D. Columbia: consultant pathologist, Rotherham and Mexborough hospitals.

The Terms and Conditions of Service of Hospital Medical and Dental Staff apply to all N.H.S. hospital posts we advertise, unless otherwise stated. Canvassing disqualifies, but candidates may normally visit the hospital by appointment.

Births, Marriages, and Deaths

BIRTHS

ABLETT.—On March 24, at Leeds, the wife of Dr. John J. L. Ablett—a son

BETTLEY.—On March 23, in London, the wife of Dr. F. Ray Bettley—a daughter.

LANGMAID.—On March 23, at Cardiff, the wife of Mr. Charles Langmaid, F.R.C.S.—a daughter.

MCMILLAN.—On March 24, in London, the wife of Dr. Ian McMillan—a daughter.

WAKELIN.—On March 24, in London, the wife of Mr. John Wakelin, F.R.C.S.—a son.

MARRIAGES

COLOVER—POLITI.—On March 9, in London, Jack Colover, M.D., M.R.C.P., to Sarina Frances Politi.

DEATHS

CROSSMAN.—On March 22, at Hambrook, near Bristol, Francis Ward Crossman, O.B.E., M.B. Durh., J.P., aged 80.

GRIFFITH.—On March 26, Patrick Gill Griffith, M.B. R.U.I., of Walton-on-Thames, aged 87.

MURRAY.—On March 24, in London, William Alfred Murray, O.B.E., M.D. Glasg., aged 88.

Obituary

EDWIN BRAMWELL

M.D., LL.D. Edin., M.D. Melb., F.R.C.P., F.R.C.P.E.

Prof. Edwin Bramwell, himself an outstanding figu of the Edinburgh medical school, was the eldest son of t late Sir Byrom Bramwell, the most renowned teacher medicine and consulting physician in Edinburgh in day.

He was born in North Shields in 1873 and educated Cheltenham College and Edinburgh University, where graduated in medicine in 1896. After the usual hous appointments, he spent some postgraduate years England, Germany, and France, and made a particul study of diseases of the nervous system at the Nation Hospital, Queen Square, London. On his return Edinburgh, he was elected F.R.C.P.E. in 1903 and settl in consulting practice. His first appointment was Leith Hospital, and in 1907 he became an assista physician to the Royal Infirmary of Edinburgh. T same year he was elected F.R.C.P. He joined his fath as an extramural lecturer and for some years taug large classes of students. During the 1914–18 war was in charge of a medical section of the 2nd Scotti General Hospital, and neurologist to the same hospit He also had charge of beds for shell-shocked patients the Royal Victoria Hospital, and for his Morison lectur at the Royal College of Physicians of Edinburgh in 19 and 1918 he took as his subject War Neurology.

Swan Walt

In 1919 he was appointed physician to the Roy Infirmary, and a year later to the lectureship in neurolo in the university. In 1922 he was called to the Moncrieff Arnott chair of clinical medicine, at the same time continuing his lectureship in neurology. His university work was heavy, but he yet found time, despite his large consulting practice, to complete his monumental work on encephalitis lethargica. He published in all over a hundred papers covering a wide field of clinical research, including chapters on the diseases of the nervous system in Allbutt's *System of Medicine*, Osler's *Modern Medicine*, *Oxford Medicine*, the *Encyclopædia Medica*, and the *Index of Treatment*. For many years he was principal medical officer to t Scottish Union and National Insurance Company, whe he succeeded his father.

Professor Bramwell held many posts of honour a distinction. He was president of the Association British Neurologists, president of the section of neurolog at the B.M.A. meeting in 1927, and president of t section of neurology of the Royal Society of Medicin For two years he was president of the Royal College Physicians of Edinburgh; and he received the honorar degree of doctor of laws from his alma mater and a honorary doctorate of medicine from the University Melbourne. In 1925 he delivered the Bradshaw lectu to the Royal College of Physicians of London, and 1937 the Croonian lectures. While on a visit to Australi in 1935 he gave the Halford oration at Canberra. A fe weeks before his death he received intimation of hi election to the honorary fellowship of the Royal Societ of Medicine. He esteemed this a high honour and th news of its award gave him real pleasure.

In his early days he took an active part in the foundation and development of the Edinburgh Postgraduat Medical School, to which he was appointed secretary i 1906, and the efficiency of the school owes a great dea to him. A. F. H. writes: "Bramwell was a stimulatin teacher, seen at his best in his clinical neurological demonstrations. He detested slipshod methods and he viewe dogmatism with suspicion unless the facts were irrefutable; but he was always willing to listen to every aspect of a problem, quickly discarding the non-essentials. No one ever came to his ward to be crammed for exams.

His diagnostic skill was of a high order and in dealing with functional cases almost approached the uncanny. His sole recreation was fly-fishing, of which art he was no mean exponent, and many a good tale he could tell of his exploits. Although handicapped by ill health for many years, he was always glad to see his friends and willing to give advice when asked. He had all the true qualities of a great physician, with an old-fashioned courtly demeanour much to be admired in these strenuous days."

W. R. R., one of his assistants, writes: "Some thousands of Edinburgh graduates must be able to look back with appreciation on Dr. Bramwell's influence on their clinical training. Though he became one of Scotland's busiest consultants, teaching in his wards was never allowed to suffer, and he taught at the Royal Infirmary, one or two hours a day, five days a week for thirty weeks a year. In addition he played a leading part in building up the organisation of postgraduate teaching at Edinburgh.

"Dr. Bramwell took pride in personally expounding the highest standards of professional conduct both as regards the consultant/practitioner and consultant/patient relationship. His careful and courteous questioning of a stupid outpatient provided a lesson which must have influenced thousands who passed through his clinics. He never embarrassed a patient by word or gesture in front of his students, and he never failed to sense when a word of reassurance was the treatment most required. He studiously avoided even a hint of 'scoring' over his colleagues when he corrected a diagnosis, so much so that often neither patient nor student realised the vital part he had played in the case. He was good at handling neurotic patients and often dramatically cured hysterical deafness or blindness by suggestion in front of his class. He was, however, almost ashamed of his skill in curing the hysterical symptoms, and would disparage his own success by remarking 'that's not medicine.'

"He expected the highest standard of work from those he trained. His house-physicians sometimes worked themselves to the stage of exhaustion, but the accurate and tireless work he expected of them probably gave them the most valuable experience of their lives. Later he watched with close interest the future careers of the many physicians he trained. At the regular end-of-term dinner-parties for his students and assistants in his charming home in Drumsheugh Gardens, he was a perfect host; and these formal but friendly parties were a fitting end to a memorable term.

"Since before the late war he had been gravely crippled with arthritis, but to visitors he seemed so much his old self that it was always a shock when he smilingly apologised for being unable to get out of his chair. He bravely maintained his interest in all things medical throughout these years, and from his study continued to play an important part in medical affairs. A special tribute should be paid to Mrs. Bramwell, who courageously mastered the endless difficulties presenting during this long illness. Those who worked with him have many impressive memories of this great and very human physician."

G. H. writes: "It is almost 50 years ago, when I was a resident medical officer at the National Hospital, that I first met Edwin Bramwell on one of his many visits. Even in these early years I was impressed by his interest in all clinical problems, and by his keenness to learn and to appreciate the views of others even on matters familiar to him. Later as I came to know him more intimately I learned to value his friendship and to recognise those abilities and features in his character which established his reputation as a physician and as a teacher of clinical medicine abroad as well as in his own country. He was essentially a clinician, painstaking and trustworthy in ascertaining his facts, and careful and logical in dealing with the conclusions that could be drawn from them. These qualities were particularly obvious in his publications in which he presented new views or new conclusions—as in his Croonian lectures on muscles, movements, and the motor paths. But by his friends, Edwin Bramwell will be remembered for his personal qualities—his friendliness and charm, his obvious honesty and simplicity, and the sympathy he extended to the work and welfare of others.

He married the eldest daughter of the late Prof. D. J. Cumming, F.R.S., and they had one son and four daughters. Professor Bramwell died on March 21.

News

University of Liverpool

At recent examinations the following were successful:

Ph.D. (in the faculty of medicine).—R. C. Nairn.

D.T.M. & H.—J. D. Bates, S. S. Chhabra, J. T. F. de Graft-Johnson, S. Kanchanagabhandh, H. B. Kennedy, Tara H. Maniar, A. R. Moore, D. A. W. Nugent, P. G. Sitwala, A. Svasti.

Dr. H. B. Kennedy and Dr. Tara H. Maniar have been recommended for the Milne medal in tropical medicine. Dr. Kennedy has also been recommended for the Warrington Yorke medal in tropical hygiene.

University of Sheffield

Dr. D. M. D. Evans has been appointed an honorary demonstrator in bacteriology.

Royal College of Surgeons

Faculty of Anæsthetists.—At the fourth annual general meeting of the faculty, held at the college on March 19, Mr. A. D. Marston, the dean, announced that Prof. E. A. Pask and Dr. W. Alexander Low had been re-elected, and Dr. M. D. Nosworthy and Dr. A. J. W. Beard elected, to the board.

Conferences on Tuberculosis and Chest Diseases

The Twelfth Congress of the International Union Against Tuberculosis and the Second International Congress on Diseases of the Chest will be held in Rio de Janeiro, Brazil, from Aug. 24 to 30. Further information may be had from Mr. Murray Kornfeld, executive secretary, American College of Chest Physicians, 112, East Chestnut Street, Chicago, 11, Illinois.

Claiming National Insurance Benefits

The following changes in the time-limits for claiming National Insurance benefits came into force on March 31:

Maternity benefit—attendance allowance.—The time allowed for claiming attendance allowance is increased from 1 month to 3 months after the date of confinement. This brings it into line with the maternity grant. These benefits can also still be claimed at any time during the 11 weeks before the expected week of confinement certified by the doctor or midwife.

Death grant.—The time-limit for a claim to a death grant by an individual is increased from 1 month to 3 months from the date of death. The time-limit for claims by local authorities and approved associations remains at 21 days from the date of death.

Time-limit for obtaining payment of benefit awarded.—The present limit of 3 months (which in certain cases can be extended to 6 months) is increased to 6 months in all cases. Postal drafts and orders in order books will still be valid for only 3 months, but an out-of-date draft or order will be replaced if application is made to the local National Insurance office within a further 3 months.

Surgical Travellers' Club

At the jubilee meeting of this club, held in London from March 26 to 29, a presentation was made to Sir Heneage Ogilvie and Lady Ogilvie in appreciation of all they had done for the club since Sir Heneage founded it 25 years ago. During the meeting visits were paid to St. Mary's Hospital, the Middlesex Hospital, Guy's Hospital, The Hospital for Sick Children, Great Ormond Street, St. Bartholomew's Hospital, and the Royal Veterinaty College. Speaking at the dinner Sir Heneage said that the members of the club included ten consultants to the Armed Forces, four members of the council of the Royal College of Surgeons of England, and the president of the Royal College of Surgeons of Edinburgh.

India's First Family-planning Clinic

India's first family-planning clinic has been opened in the Lodi Colony, New Delhi, by Dr. K. C. K. E. Raja, director-general of health services, Ministry of Health. The Lodi Colony was chosen as it is a compact area with a closed population, which can be kept under observation. The clinic, which is in the charge of one full-time doctor assisted by two health visitors and two medical social workers, will instruct the residents seeking its help in the rhythm ("safe period") system of family planning, to popularise which Dr. Abraham Stone, of W.H.O., recently toured various parts of India. Pilot studies in this method are to be initiated in other centres, to determine its suitability for general introduction throughout the country. At the suggestion of Dr. Stone, the Indian Council of Medical Research is to set up a committee to foster research in the medical and technical aspects of human reproduction.

Congress of Neuropathology

The final programme will shortly be available of the first International Congress of Neuropathology, which is to be held in Rome from Sept. 8 to 13. Those who wish to join the British party to the Congress should write to Dr. J. G. Greenfield at the National Hospital, Queen Square, London, W.C.1, as soon as possible.

Seminar on World Health

The fourth seminar on world health to be held by the World Federation will take place in Geneva from May 5 to 17, during the World Health Assembly. It is open to doctors, medical students, and others interested in public health. The speakers will include Dr. Pierre Dorolle, Dr. G. R. Hargreaves, Dr. Marcelmo Pascua, Dr. Robert Burgess, and Dr. W. P. Forrest. Applications may be sent to the offices of the federation, UNESCO House, 19, Avenue Kléber, Paris, 16.

Director-General, Army Medical Services

On April 1 Lieut.-General Frederick Harris, C.B., C.B.E., M.C., M.B., took up his appointment as Director-General, Army Medical Services, in succession to Lieut.-General Sir Neil Cantlie.

Lieut.-General Harris was educated at Coleraine School and Trinity College, Dublin, qualifying in 1914. He was first commissioned in the R.A.M.C. in January, 1915, and served in France, [illegible] during the 1914–18 war. He was [illegible] spatches, and was awarded [illegible] in hygiene, and obtained [illegible] was assistant professor of [illegible] College. He was Deputy Director of Hygiene and Pathology, G.H.Q., India, from 1941 to 1945, and he revised *The Field Hygiene Pocket Book, India*, a manual which served as a guide to innumerable medical officers in eastern theatres during the late war. In 1946 he became Deputy Director of Medical Services, Burma Command, and in 1947, as Director of Medical Services, Middle East Land Forces, he undertook the reorganisation on a peace-time basis of the medical arrangements in the Army's largest overseas theatre. He has been Deputy Director-General, Army Medical Services, since 1948. He became a C.B.E. in 1944 and a C.B. in 1949. He was appointed an honorary surgeon to the King in 1946.

Institute of Almoners

Addressing the annual general meeting of this institute in London last Saturday Miss M. P. Hornsby-Smith, parliamentary secretary of the Ministry of Health, spoke of the need to make more effective use of hospital beds and outpatient facilities, and said that the almoner could do as much as anyone to ensure that the resources of the hospitals are used economically. "Yours," she said, "is essentially a human service, a skilled service, and a vital one."

With Prof. Alan Moncrieff as chairman, members of the institute and their guests much enjoyed the annual dinner on the same evening. Proposing the toast of The Institute, Sir Cecil Wakeley, P.R.C.S., recalled the difficult case of one of his patients who was restored to health only to find that his wife (hearing he had but three months to live) had removed his clothes and married someone else. "Of course," said Sir Cecil, "I turned it over to the almoner, and everything ended happily." He thought that almoners were too much inclined to work in silence or by correspondence: they did not do enough walking round to see the physician or surgeon. Miss M. Perfect, responding, recalled that the first almoner was appointed to a hospital in 1895. The advertisements of 100 unfilled jobs every month unsettled the profession, she thought: might it not be better to suppress them and let almoners advertise their services—and requirements? She mentioned that one of her juniors had come to her lately in great distress, saying: "I am a traitor to my profession. I don't know what case-work is." "Never mind," Miss Perfect had replied, "I don't know either. It seems better to forget all about it and just carry on." Miss E. Cohen, as a social worker from the United States, spoke of the almost palpable change that had come over this country in the fifteen years since her last visit; but she did not go into details. In the U.S.A., she said, the trend of social workers was towards a single organisation, preserving what was significant in the specialties. Miss E. Perkins engagingly proposed The Guests, of whom Miss G. M. Aves, of the Ministry of Health, replied. Though glad to be described as "of Whitehall" she admitted that her department now worked over the china shop in Regent Street; but "it remains," she said, "as remote, and uninformed about the world, as ever." Her further remarks suggested that this might be an over-statement.

Medical Art Society

The annual exhibition of members' work will be held Walker's Galleries, New Bond Street, London, W.1, fi April 21 to May 3.

Operation before a Public Television Audience

In Philadelphia the public have been enabled, by me of television, to see an operating-theatre during the last minutes of an operation for peptic ulceration. The N York Times (March 17) reports that the station wh sponsored the broadcast received such comments as "T is the television we've been waiting for." "Was the pati real?" "It was thrilling."

An International Journal of Nutrition

The Nutritional Press of Allentown, Pennsylvania, h announced the forthcoming publication of a new bi-mont international journal, the *Journal of Clinical Nutriti* which is to be devoted to "the practical application of newer knowledge of nutrition." The contents are to incl original papers, review articles, and an integrated abstr section. The editor-in-chief is Dr. S. O. Waife of Ph delphia, and Sir Edward Mellanby, F.R.S., is the correspond editor for England and Dr. A. P. Meiklejohn for Scotla Further information may be had from the journal at 1 South 36th Street, Philadelphia, 4, Pennsylvania.

EMERGENCY BED SERVICE.—In the week ended 1 Monday applications for general acute cases numbered 9 The proportion admitted was 90·2%.

CORRIGENDUM.—We regret that on p. 648 last week the t of *Diagnosis of Nervous Diseases*, by the late Sir James Purv Stewart and Dr. C. Worster-Drought, was wrongly given

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Prof. A. A. Moncrieff has been elected to the Académie Nation de Médecine in Paris as a *correspondant étranger*.

Diary of the Week

APRIL 6 TO 12

Monday, 7th

INSTITUTE OF PSYCHIATRY, *Maudsley Hospital, Denmark Hill, S.I*
5.30 P.M. Dr. K. Cameron: Lecture-demonstration.

Tuesday, 8th

ROYAL COLLEGE OF SURGEONS, Lincoln's Inn Fields, W.C.2
3.45 P.M. Mr. A. T. Andreasen: Aortic Arch Anomalies. (Fi of two Erasmus Wilson demonstrations.)

ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W.1
8 P.M. *Section of Psychiatry.* Prof. J. Lopez Ibor (Madrid Recurrent Anxiety States and their Treatment by Acet choline.

ROYAL EYE HOSPITAL, St. George's Circus, S.E.1
5 P.M. Prof. Arnold Sorsby: Genetics in Ophthalmology.

SOCIETY FOR THE STUDY OF ADDICTION
4 P.M. (11, Chandos Street, W.1.) Dr. W. R. Bett: Willi Stewart Halsted (1852–1922): Cocaine Pioneer an Addict.

Wednesday, 9th

ROYAL COLLEGE [illegible]
3.45 P.M. Mr. [illegible] Pulmonic Flow. (Seco of two [illegible] trations.)

ROYAL SOCIETY OF MEDICINE
4.30 P.M. *Section of Physical Medicine.* Sir Hugh Griffiths, D A. A. Eagger: Industrial Resettlement.

ROYAL EYE HOSPITAL
5.30 P.M. Mr. Howard Reed: Visual Fields.

INSTITUTE OF NEUROLOGY, National Hospital, Queen Square, W.C.
5 P.M. Professor Lopez Ibor: Agoraphobic Giddiness.

SOCIETY OF CHEMICAL INDUSTRY
6.30 P.M. (Burlington House, Piccadilly, W.1.) *Food Group.* Pro Ancel B. Keys (Minnesota): Health and Diet in th Western World.

Thursday, 10th

INSTITUTE OF PSYCHIATRY
3 P.M. Dr. Hudson Hoagland: Adrena Cortex Function i Normal and Schizophrenic Men.

HONYMAN GILLESPIE LECTURE
5 P.M. (University of Edinburgh.) Dr. W. Ritchie Russell Poliomyelitis.

[illegible] Dundee.) Prof. R. W. B

THE PATHOLOGY AND TREATMENT OF PORTAL HYPERTENSION*

R. MILNES WALKER
M.S. Lond., F.R.C.S.
PROFESSOR OF SURGERY IN THE UNIVERSITY OF BRISTOL

To determine what we mean by portal hypertension it is necessary to know the normal limits of the blood-pressure in the portal circulation, and it is only recently that such records have been made in man; all the observations are based on measurements made under the artificial conditions of laparotomy, and should be checked with the systemic blood-pressure at the time, and with the pathology of the liver, because other conditions, apart from fibrosis, may influence the portal blood-pressure.

When I refer to portal hypertension I mean an abnormally high pressure in the whole of the portal circulation, and this excludes those cases where there is obstruction to the splenic vein, which I prefer to call splenic hypertension.

My colleagues and I have observed the portal pressure of 20 patients during operations for conditions other than liver disease, and these figures range from 85 to 150 mm. of water, the measurements being taken with a water manometer or a condenser manometer connected to a needle or a cannula in a tributary of the portal vein. Three of my patients who had œsophageal varices, which may be taken as evidence of portal hypertension, had pressures of 180 mm. of water, and I regard 150 mm. of water as about the upper limit of normal, though Gray (1951) regards 210 mm. of water as the upper limit. He has taken the anterior border of the lumbar vertebræ as his base-line, whereas in my series the level of the portal vein was taken as zero, but this hardly explains the difference in our records. Three cases of obstructive jaundice had pressures of 210, 210, and 175 mm. of water; in a case of amyloid disease of the liver a pressure of 280 mm. of water was found; and a man with extensive hepatic metastases from a carcinoma of the stomach had a pressure of 310 mm. of water.

Probably in health the portal blood-pressure undergoes considerable variation in association with changes in the blood-flow through the abdominal viscera and influences acting on the vessels in the liver itself, and readings taken with the abdomen open at operation must be regarded as only approximate.

CONSEQUENCES OF PORTAL HYPERTENSION

An extensive collateral circulation develops as a result of portal venous obstruction, but it is only in the lower end of the œsophagus and adjacent stomach that it is dangerous to the patient; all the other collaterals are beneficial in providing relief from the obstruction, and there is evidence that this relief may be an important factor in saving the patient from a dangerous hæmatemesis. I suspect that, provided a patient has no disease of the liver which is progressive, he may in time develop an adequate collateral circulation to drain off all the portal blood, and this is confirmed by the knowledge that patients may survive with complete thrombosis of the portal vein. If the calamity of a fatal hæmorrhage from the œsophagus can be averted, there is no reason why such patients should not survive for many years, and I think this state of affairs explains some of the examples of splenomegaly which are quite symptomless. The following is such a case.

Case 1.—A woman, aged 36, had been diagnosed as having Banti's syndrome at the age of 16, and records confirm that she had an enlarged spleen at that time. She has since given birth to 3 children, but when I saw her she still had an enlarged spleen. At laparotomy for another condition her portal pressure was found to be 180 mm. of water, her liver was moderately cirrhotic, and œsophagoscopy showed a few œsophageal varices. I suspect that many years ago her portal pressure had been considerably higher, but that she had developed a natural venous shunt which had brought it down to a safe level.

The size of the spleen in these cases is not due to simple congestion (Himsworth 1950a) and does not give an indication of the level of portal pressure. Portal hypertension by itself does not cause ascites, which, when present, indicates severe damage to the liver; most of my patients who have had really high portal pressures have had no free fluid in the abdomen.

The clinical diagnosis usually rests on the demonstration of varicosities in the submucous plexus of veins in the œsophagus; these may be shown by X rays after a barium swallow, but œsophagoscopy is a much more reliable method of detecting them and should always be done in suspicious cases if the X rays do not reveal them.

PATHOLOGY

As pointed out by Whipple (1945), the obstruction which causes portal hypertension may be prehepatic, intrahepatic, or posthepatic; only the first two groups will be considered here.

Prehepatic Obstruction

In this group the blood-flow is obstructed in either the portal vein itself or its main branches in the liver. Cases secondary to pressure from without need not concern us, and thrombosis of the portal vein in the absence of fibrosis in the liver is very rare. In my series are 9 cases of prehepatic portal obstruction, in all of which the symptoms first appeared in childhood. Published reports of such cases show that the abnormality is either a simple stenosis of the portal vein or an atresia of variable length, or the place of the vein is taken by a mass of dilated vascular spaces which extend some way along the portal tracts into the liver—the condition known as cavernomatous transformation of the portal vein. These states are probably true congenital abnormalities. Of my patients only 1 has died, and I am grateful to Prof. Jethro Gough, of Cardiff, for letting me see the necropsy and for the histological preparations. This was a true case of cavernomatous change. At laparotomy a year before death the place of the portal vein was found to have been taken by three tortuous thin-walled channels which communicated with each other; at necropsy the liver parenchyma appeared normal, but the portal tracts contained wide venous channels which, in the larger tracts, were so extensive as to give the appearance of an angioma; only injection methods would have shown whether they had any actual communications with the sinusoids.

In all these cases of prehepatic obstruction the liver looked and felt normal and was normal histologically, and it is this fact which classifies them as prehepatic obstruction, for the abnormality of the portal vein may be high up in the portahepatis and not recognisable at operation. Apart from the case already mentioned, the site of the portal vein has been closely examined in 3: in one case the lower part of the vein was normal and was used for an anastomosis; in the second case the vein felt thrombosed; and in the third the place of the vein was taken by varicose channels.

Clinically the only symptom of this type of case is hæmatemesis from œsophageal varices, and published reports suggest that the patients all die from this cause early in life. In my 9 patients the bleedings started at the age of 3–14 years, average 9 years. The portal pressures were measured in 8 of them, and in 6, who at the time of measurement had had no previous operation, they were 300–450 mm. of water, average 386 mm.; and in 2 who had had their spleens removed at a previous operation the pressures were 250 and 260 mm. of water. 5 of these patients had undergone splenectomy before I saw them, and I am grateful to the surgeons who recorded the pressures in 3 of them and have let me know their findings. I doubt if there is any significance in the fact that lower pressures were recorded in the other 2, since we do not know what their pressures were before splenectomy, but in not one of the 5 did the operation prevent further bleeding.

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* From a University of London lecture delivered at Westminster Hospital on Feb. 26, 1952.

Intrahepatic Obstruction

It became clear early in this investigation that the patients with intrahepatic obstruction fell clinically into two fairly distinct groups: those who presented with hæmorrhage from œsophageal varices as the leading or only symptom, and those who had ascites or other evidence of disturbance of liver function. When opportunity arose an attempt was made to correlate the symptoms with the portal pressures, and, as would be expected, those who bled had, on the whole, the higher portal pressures. Apart from some cases with rather peculiar ætiology, the pressures in 21 who bled from the œsophagus and had practically *no other symptoms* were 200–560 mm. of water, average 360 mm. Fewer opportunities for measurement occurred in the ascitic group, but records in 7 ranged from 130 to 365 mm. of water, average 230 mm.

These pressure readings have also been related to the gross appearance of the liver seen either at laparotomy or through the peritoneoscope; in the group who bleed all types of liver surface have been noted, but the most characteristic one is that in which the liver is a little firmer than normal, about normal in size, and with a finely granular surface showing slightly raised areas up to 2 mm. in diameter but without gross scarring; such a liver may feel almost normal when palpated with the hand at laparotomy, and the surgeon may not appreciate the true state of affairs. On the other hand, in this group the liver may show coarse scarring with a nodular surface, the nodules being up to 2 cm. in diameter and separated by either shallow depressions or deep furro When ascites is present, the liver is always scarred, a the abnormality is easily recognised.

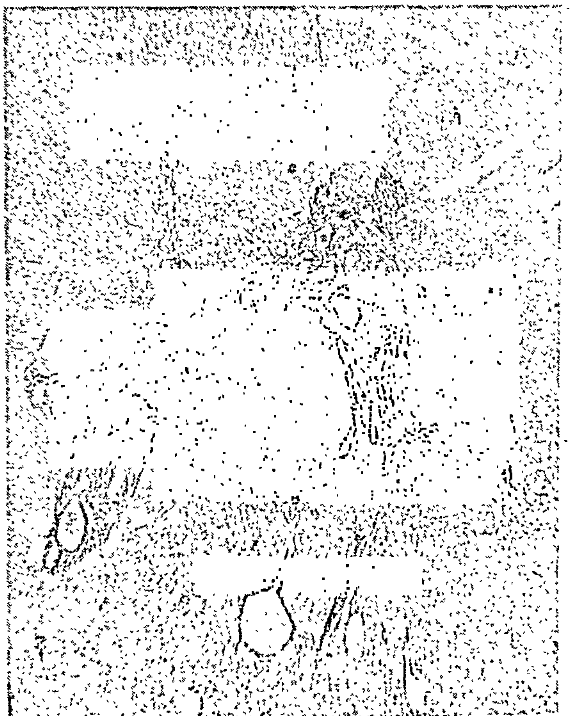

Fig. 1—Type-I portal hypertension, showing fibrosis confined to portal tracts (case 2). (× 40.)

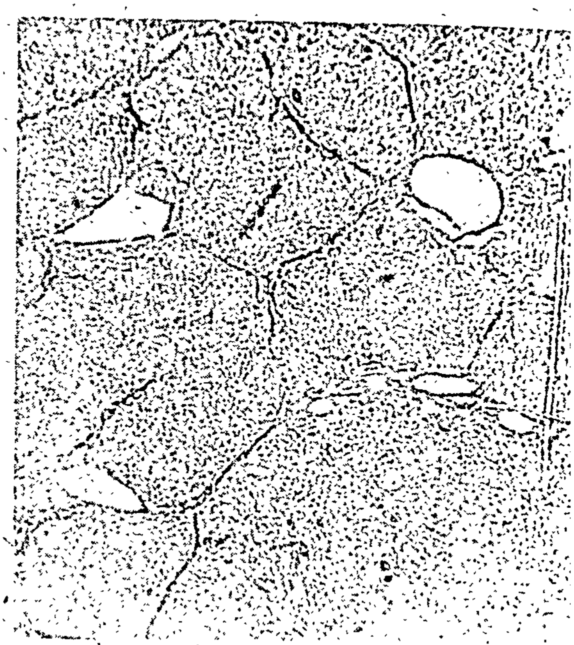

Fig. 2—Type-II portal hypertension, showing fine strands of connec tissue linking portal tracts and central veins (case 3). (× 40.)

Histology of Liver

The gross appearances suggest that the level of por pressure is not proportional to the amount of fibrosis the liver, and the histology bears this out. Among t cases of intrahepatic obstruction the microscopic appe ance is available in 43 and the distribution of the fibro tissue has been noted; these cases fall into three i defined types with all intermediate appearances.

The *first type* shows only an increase in the fibro tissue in the portal tracts, but these tracts appear mo circular than normal, as if the fibrous tissue was co stricting them; the intervening parenchyma appea normal, and the central veins are not involved. T following is an example of this type:

Case 2.—A woman, aged 48, had a hæmatemesis in Augu 1950, and further attacks in November, 1950, and Decemb 1951, the last attack requiring transfusion of 4 pints of bloo The spleen was enlarged to 4 finger-breadths, liver-functi tests were normal, and œsophageal varices were present. operation her portal venous pressure was 270 mm. of wat and a portacaval shunt was made. Biopsy of the liver show fibrosis confined to the portal tracts (fig. 1).

In the *second type* the fibrous tissue is not so close confined to the portal tracts but spreads out as fi strands into the liver parenchyma and may go so far to link up one portal tract with its neighbours and wi the central veins. In fact, this is what has been describ by Himsworth (1950b) as the earlier stages of diffu hepatic fibrosis.

Case 3.—A man, aged 26, had a severe hæmatemesis August, 1950, and on examination the spleen was enlarged 4 finger-breadths, and large varices were present in th œsophagus. When a portacaval anastomosis was done, th liver was of normal size but showed a slightly nodular surfac The portal pressure was 330 mm. of water and the portal vei healthy. Biopsy showed fibrosis of the portal tracts, whic were linked to neighbouring tracts by thin strands of fibrou tissue (fig. 2).

In the *third type* the liver structure seems to be com pletely disorganised; bile-ducts, arteries, and veins ar present in masses of fibrous tissue, which in a section ma occupy as much as half the field; central veins whic an be recognised are difficult to find, but the connective issues contain many thin-walled vascular channels; the ppearance is that of postnecrotic scarring (fig. 3). These atients may belong to either of the two clinical groups, ut ascites and other signs of failure of liver function are ften present; in fact, the prognosis is serious, and the atient may die as a result of liver failure. The portal ressure in those cases with grossly scarred livers is sually moderately raised, but there is one such case with grossly scarred liver with a normal pressure of 130 mm. f water, and another at the other end of the scale with pressure of 470 mm. of water.

I have been careful to call attention to these three ypes because I am convinced that they are not stages in continuous process; many of the third type, with gross ibrosis, have only a short clinical history, whereas atients of the first two types, when bleeding from the esophagus is as a rule the only symptom, may live for nany years without any evidence of deterioration of iver function.

Case 4.—A man, aged 36, with no history of jaundice, had æmatemesis in 1940, 1945, and 1948. Large varices in the esophagus were demonstrated radiologically, and on laparoomy the liver showed the typical granular appearance of liffuse hepatic fibrosis. The portal pressure was 400 mm. of vater, and at that time nothing was done except ligature of the splenic artery.

In 1951 his varices were still large, and the portal vein was explored when the pressure was only 220 mm. of water, and the vein was found to be completely thrombosed. The histology of the liver showed the same appearance as that found two years previously. Subsequently an œsophageal transection was done, and a year after this the patient writes to say that he is very well. At the time of his second operation liver-function tests showed no abnormality except a thymol turbidity of 4 units.

If we accept the view (Dible 1951) that in this country most cases of hepatic fibrosis are the result of acute hepatitis, is it possible to explain the different types which have been described? The early lesions in acute hepatitis, according to Dible et al. (1943), consist, in the mild cases, of an accumulation of inflammatory cells in the portal zones, but in the more severe cases central necrosis also occurs. If the fibrosis results from the organisation of inflammatory cells, it follows that, if the reaction is confined to the portal tracts, the first type will result; but, if the inflammation extends into the parenchyma, so will the subsequent fibrosis, and the second type follows; if the original attack is so severe that it causes not only periportal inflammation but also central necrosis and the patient survives the illness, then postnecrotic scarring will be the inevitable result, and this is the picture found in the third type of case. What I wish to emphasise is that one type does not progress into the next, but that the ultimate pattern in the liver depends on the site and extent of the original liver damage.

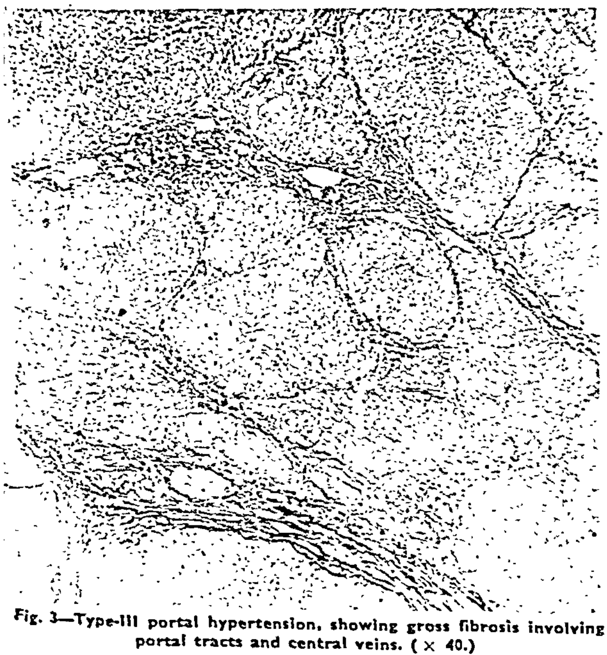

Fig. 3—Type-III portal hypertension, showing gross fibrosis involving portal tracts and central veins. (× 40.)

Relation of Pathology to Symptoms

It is necessary also to look for an explanation of the symptoms in these three types of hepatic fibrosis. We know, as a result of observations on the cases with prehepatic obstruction, that the liver remains normal, histologically and functionally, for many years when deprived of its portal blood; the results of end-to-side portacaval anastomoses also indicate the same thing. Therefore functionally the first type is akin to the prehepatic obstructions in showing no evidence of disturbed liver function, and in having really high portal pressures. In the second type—diffuse hepatic fibrosis—there may be some compression of the liver parenchyma, but here also liver function is not seriously impaired, though portal pressures may reach high levels; in long-standing cases there is time for an extensive collateral circulation to develop between the portal and systemic circulations, and this may lead to some reduction in the pressure, as probably happened in the case already described, where the patient was known to have had the disease for twenty years and the pressure was only 180 mm. of water.

One of the characteristics of the third type, those with postnecrotic scarring, is that the fibrous tissue is often very vascular, and the central veins are involved in the fibrous network. Thus these veins are liable to be constricted, causing congestion in the sinusoids, and this may be an important factor leading to disturbance of liver function. In other words, if the obstruction is presinusoidal, liver function is unimpaired provided that an adequate supply of blood from either the hepatic artery or the portal vein still reaches the sinusoids; but if there is also postsinusoidal obstruction causing congestion in the sinusoids, ascites and other signs of defective liver function appear. We know that posthepatic obstruction, such as occurs in constrictive pericarditis, leads to fibrosis in the liver. Therefore in the third type of hepatic fibrosis, in which the central veins are obstructed, we should expect the disease to be progressive, and such is in fact the case.

TREATMENT

Patients with portal hypertension die as a result of hæmorrhage from the varices which develop in the œsophagus and the upper part of the stomach. Those with prehepatic obstruction rarely reach adult life. Those with intrahepatic obstruction may also die as a result of the interference with the function of the liver, and in these cases the patient may be rendered most uncomfortable by ascites, which complication may contribute to death. Though it has been demonstrated time and again that patients with a normally functioning liver may have very high levels of portal blood-pressure without ascites, the results which Blakemore (1951) has obtained by portacaval shunts seem to indicate that, when the liver is damaged, the high portal pressure does have an influence in aggravating the accumulation of fluid in the peritoneal cavity. The great aim of surgical treatment is to reduce the risk of bleeding from the collateral vessels, but in those cases in which fibrosis in the liver is accompanied by a high portal pressure and ascites there may possibly be an indication for surgical measures which will bring down this pressure.

The pioneer work of Whipple (1945) and Blakemore and Lord (1945) has led to a revival in the use of venous shunts to carry the portal blood back into the systemic circulation. Apart from the operative mortality, which depends largely on the proper selection of cases, these venous anastomoses are liable to be occluded by thrombus. My own experience has led me to take the view that, unless an opening larger than 1 cm. in diameter can be made, the risk of its becoming occluded is so great that it is hardly worth attempting. I know that in one of my early cases the shunt became occluded, and I suspect that some of the others have suffered the same fate. However, the production of a large vascular shunt is the only radical way of bringing down permanently the portal blood-pressure, and Blakemore's (1951) results fully justify the operation. He claims that the average fall in portal pressure following the shunt is 200 mm. of water. Though several different veins in the portal circulation have been used, he finds that his best results follow a shunt between the portal vein and the inferior vena cava, and my own smaller experience bears out this view. Often, however, particularly in cases of prehepatic obstruction, the abnormality of the portal vein prevents its use for this purpose, and the next alternative is a shunt between the splenic and left renal veins. I have felt from the start that it was not justifiable to remove a healthy kidney to make such an anastomosis, and in all my series the kidney has been preserved, the anastomosis being either end-to-side or in a few cases side-to-side, the spleen being left in place. The first of these end-to-side splenorenal shunts was made in May, 1947, with a 'Vitallium' tube. This patient is still in good health, but I suspect that his shunt has become occluded, and he has since had a palliative operation on his œsophageal varices. In cases of prehepatic obstruction, in which the portal vein is usually unsuitable for a shunt, it is unfortunate that so often the spleen has been removed, and thus the only alternative vein is also lost. This had happened in 5 of the 9 cases in this group which have been referred to me. I have on two occasions used other vessels for the shunt, but their use is not recommended, because only the portal and splenic veins are of really adequate size.

My early attempts at portacaval shunts were made by approaching the portal vein from the front through an incision in the anterior abdominal wall, but many difficulties were encountered. Either the extensive collateral veins around the common bile-duct prevented the vein from being exposed at all; or when the vein was dissected out it was so deep down that making the anastomosis was difficult and hazardous. These factors led me to abandon the operation for a time, but rather more than a year ago I attempted the transthoracic approach, going through the right pleura and diaphragm, and found that this made all the difference to the operation. Since then I have made 10 portacaval anastomoses by this route, 9 being end-to-side and 1 side-to-side with a vein graft, without any difficulty and with most satisfactory results. In only 2 cases have I approached the vein by this route and failed to make an anastomosis; one was a congenital case in which the portal vein was cavernomatous, and in the other the vein was completely thrombosed.

With experience the proportion of cases in which a shunt can be done increases, but there are bound to be some in which no suitable vein is available, and thus the possibility of palliative operations has to be considered. I have already indicated that in many of these cases the pathological condition in the liver is either static or only very slowly progressive, and that these patients develop a collateral circulation which may eventually drain away all the portal blood and may, I suspect, lead to some reduction in portal pressure. It therefore seems that palliative operations which will prevent the patient from dying of hæmorrhage during the period that other collaterals are forming have a place in the treatment of this condition and are worth while if the danger of a fatal hæmorrhage is great. I have tried many of these methods.

Ligature of the splenic artery alone, or *removal of the spleen* gave disappointing results; the former certainly does no harm, but I believe that splenectomy alone may actually increase the risk of hæmorrhage by removing some of the natural collateral circulation which has developed in the attachments of the spleen, though the operation may be necessary if there is evidence of hypersplenism.

Omentopexy also gives very doubtful benefit and has been generally abandoned.

I have no experience of *ligature of the hepatic artery* as advocated by Rienhoff (1951); but this is an interesting experiment, and its success may depend on the free anastomosis between the hepatic artery and the portal vein which develops in the fibrous tissue in the liver in severe cirrhosis.

Tanner (1950) drew attention to operations which would cut off the portal blood flowing to the œsophageal varices, and I did a few of the *gastric transections* whi he described, but access was not always easy, becau there were often extensive vascular adhesions.

Œsophageal Transection.—As an alternative I took doing a similar operation through the left pleural cavit exposing the lower end of the œsophagus, cutting across and resuturing it after ligaturing the larg submucous varices, thus forming a line of scar tiss across which, no doubt, varices re-form; but it may gi time for a more adequate collateral circulation to for elsewhere. The first case was in a man, aged 32, who h had hepatitis seven years before; he had two very seve hæmorrhages at a month's interval, and had a port pressure of 490 mm. of water. The intense congestion the tissues around the stomach and pancreas ma either a splenorenal shunt or a gastric transectio impossible, so at a second operation a lower œsophage transection was done through the left chest. That w sixteen months ago, and the patient has remained we since, though he has changed his occupation, which wa formerly that of a publican. It is still too early to clai any definite results for this operation, which has been don on 6 patients in the last two years, but only 1 of them ha had a further hæmorrhage; it is, I think, at least effective as some of the more extensive operations th have been done on the œsophagus.

The 73 cases which form the basis of this study hav been classified as follows:

	No. of cas
Prehepatic obstruction	9
Hepatic fibrosis of unknown ætiology	46
Hepatic fibrosis associated with:	
Congenital atresia of bile-ducts	1
Amyloid disease	1
Hæmochromatosis	1
Polycythæmia	1
Hepatic fibrosis following an illness with jaundice, presumably acute hepatitis	11
Hepatic fibrosis following treated syphilis ..	2
Unconfirmed pre- or intra-hepatic obstruction ..	1

In most of the cases œsophageal varices were demonstrated by X rays or œsophagoscopy, and in nearly all of them liver-function tests were done. Portal pressures in the 42 in which it has been measured ranged from 130 to 560 mm. of water, the 1 case in which it was within normal limits having a grossly scarred liver.

Major surgery to reduce the venous pressure, either in the whole portal system or in the œsophageal varices, was done in 49, more than one such operation having been done in 8 cases. The operations are shown in the accompanying table.

TYPES OF OPERATIONS DONE

Type of operation	No. of operations	Operative deaths	Later deaths	Patients alive with recurrence of symptoms
enectomy	7	2	1	2
enic artery ligation ..	11	1	1	3
Total	18	3	2	5
al-systemic shunts :				
End-to-side portacaval	9	..	..	1
Side-to-side portacaval	3	..	1	1
End-to-side splenorenal	10	3	..	2
Side-to-side splenorenal	3	..	1	1
Other vessels	2	..	..	..
Total	27	3	2	5
nsections :				
Gastric	4	..	..	2
Œsophageal	6	..	..	1
Total	10	..	..	3
ature of veins ..	2	..	..	..
Grand total ..	57	..	..	..

addition, splenectomy had been performed in 8 cases efore I saw them, and an end-to-end splenorenal nastomosis in 1; there was recurrence of hæmorrhage every one of these. Splenectomy alone and splenic- tery ligation have already been referred to as useless, cept in special circumstances, and were given up two ears ago.

RESULTS OF SURGICAL TREATMENT

It is still too early to assess the late results of œso- hageal transection; at best it can only be regarded as alliative.

The group of 27 patients who have had shunts provide more interesting study; it is appreciated that, before dequate experience of the technique had been obtained, any of the openings were too small and others were adly placed, and one or two of the early cases were nsuitable from the point of view of general condition nd liver function.

The 3 operative deaths were all in the first 7 cases of e series, and there has been no operative mortality ince September, 1948; 2 were caused by leakage at the ture line, and the 3rd by mesenteric thrombosis.

The 3 cases of splenorenal anastomosis in which the mptoms recurred were also early cases where the pening was considered at the time barely adequate, and robably the shunt is closed.

The patient in whom symptoms recurred after anas- omosis of other vessels was originally operated on in ecember, 1947. She had prehepatic obstruction and ad already lost the spleen; her right ovarian vein as anastomosed over a vitallium tube to the side of he portal vein. She has had no more bleeding, but, ince her œsophageal varices remained very large, an esophageal transection was done, in March, 1951, and he is now married and expecting her first baby shortly.

One of the later deaths was in the child with prehepatic bstruction already referred to, who died of hæmorrhage rom the œsophagus a year after one of the cavernomatous hannels had been anastomosed to the inferior vena cava; he vein was really unsuitable for this purpose, and it is ot surprising that the opening became closed by hrombus.

The second later death was of a patient, aged 66, whose ain symptom was ascites, and she had a splenorenal nastomosis; the opening was unsatisfactory because an verting suture was not used, and thrombosis probably ccurred. The patient died at home of hepatic failure 2½ years later, having been tapped three times in this interval. The operation, in the light of further experience, would not be recommended at her age for ascites.

INDICATIONS FOR SURGICAL TREATMENT

I regard the indication for surgical treatment as severe hæmatemesis from œsophageal varices, or the likelihood of such bleeding as indicated by the presence of large varices. I am doubtful about its value for the relief of ascites, and my experience of hepatic cirrhosis as seen in this country is that, if ascites cannot be controlled by dietetic measures, the liver function is so impaired that major surgery is rarely justifiable.

It is now my policy to explore the portal vein through an incision through the right thorax and to measure the portal pressure. If this pressure is significantly raised and the portal vein is healthy, a portacaval shunt is made, preferably end-to-side after division of the vein high up in the hilum of the liver. If the case is one of prehepatic obstruction and the portal vein is abnormal, at a second operation the splenic vein is exposed and a splenorenal shunt made. If the splenic vein is large and can easily be approximated to the renal vein, a side-to-side anastomosis is made and the splenic artery tied, but the spleen is left in place; often this is impossible and it is necessary to remove the spleen and make an end-to-side anastomosis. If neither of these operations is possible, as may be the case, particularly if the spleen has already been removed, then an œsophageal transection is done through the left pleural cavity.

SUMMARY

Portal hypertension may be due to prehepatic, intrahepatic, or posthepatic obstruction. The causes of prehepatic obstruction are usually congenital. Intrahepatic obstruction may be presinusoidal or postsinusoidal, and the latter causes impairment of liver function. The pattern of fibrosis following acute hepatitis is determined by the extent of the original inflammation; when it is presinusoidal, the condition may remain stationary for many years.

Venous shunts have a definite place in the treatment of portal hypertension; an end-to-side portacaval shunt is the most satisfactory if it can be done; and in view of the serious risk of fatal hæmorrhage in these cases, particularly in young people, the operative risk is not excessive, there having been no deaths in the last 20 cases in this series. It is as yet too early to know whether the palliative operations now being done on the œsophagus justify themselves; but, when bleeding has been dangerous, they are worth a trial. Finally, in portal hypertension splenectomy alone should never be done; it does not reduce the risk of fatal bleeding, and it may destroy the only vein which is available for an anastomosis.

REFERENCES

Blakemore, A. H. (1951) *Bull. N.Y. Acad.* 27, 477.
— Lord, J. W. jun. (1945) *Ann. Surg.* 122, 476.
Dible, J. H. (1951) *Brit. med. J.* i, 833.
— McMichael, J., Sherlock, S. P. V. (1943) *Lancet*, ii, 402.
Gray, H. K. (1951) *Ann. R. Coll. Surg.* 8, 354.
Himsworth, H. P. (1950a) Lectures on the Liver and its Diseases. 2nd ed., Oxford; p. 14.
— (1950b) *Ibid*, p. 54.
Rienhoff, W. F. jun. (1951) *Bull. Johns Hopk. Hosp.* 88, 368.
Tanner, N. C. (1950) *Proc. R. Soc. Med.* 43, 147.
Whipple, A. O. (1945) *Ann. Surg.* 122, 449.

"... Most men find the problems of political power insoluble and tend to despair before a world that has shrunk in scale and enlarged in complexity, so that the knowledge of how it behaves seems more and more to be open only to the specialist. There never was a time, except perhaps in the fearful pestilences of the Middle Ages, when men hungered more for a decent private life, and when they are tempted to match in their joys the intensity of the sorrows all around them. I believe that this impulse, far from being an escape, is the only right way of asserting that human dignity which gives sense to the phrase 'an appetite for life.' What reasonable hope can an ordinary man have for himself and his family? Must we oscillate like crocodiles between panic and apathy? What more adult way is there of coming to terms with the alternatives of the atomic age?"—ALISTAIR COOKE. *Letters from America.* London, 1951, p. 19.

INCOMPATIBLE TRANSFUSIONS

THEIR CAUSES AND PREVENTION

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BLOOD-TRANSFUSION saves the lives of patients with severe hæmorrhage; but every transfusion carries a risk of hepatitis (0·8%), of incompatibility, and of infection. In December, 1946, I undertook the responsibility for the organisation of transfusion services within the Central Middlesex Hospital; and this paper is a report on the principles followed, the technique employed, and the misadventures encountered. It is based on the results of transfusion of about 10,000 bottles (5000 litres) of blood on some 4000 occasions over a period of exactly five years.

The hospital serves a compact population of some 300,000. About 150 patients with hæmatemesis and 500 with abortion are admitted each year; about 40% of the blood transfused is used by the department of gastroenterology, and 20% by that of gynæcology and obstetrics, which maintains a flying squad. During the first few months it became obvious that many of these patients needed emergency transfusion as soon as possible—some because their blood volume had sunk to dangerously low levels, and others because they had become seriously anæmic and were still bleeding. Since large-pool plasma carried up to a 12% risk of hepatitis, and small-pool plasma, now known to carry a much smaller risk (Lehane et al. 1949), was still being tried, the demand was for whole blood to be ready within a few minutes.

It is impossible to supply whole blood within a few minutes without running the risk of giving incompatible blood. It takes at least three hours to perform all the tests required to exclude every variety of incompatibility. At that time it was believed that the mortality of incompatible transfusion was about 50%, but that the ABO and Rh systems were the only ones of clinical importance; so it was decided to attempt to make ABO and D(Rh$_0$) homologous blood available at thirty minutes' notice throughout the day and night. I had formed the opinion that for many of our patients a delay of one and a half to two hours would prove more lethal than would the incompatibilities which might occur.

Subsequent work has made little difference to this opinion. Race and Sanger (1950) list only 45 known antisera to N, S, Lutheran, Kell, and Duffy; and though antibodies to M and to Lewis are more common they seem to cause transfusion reactions of fairly mild type, which would not be lethal if the patient were carefully watched during transfusion. Rhesus antibodies of the rare types produced by rhesus-positive persons number less than 1% of all rhesus antibodies.

The policy adopted was based on these principles. A transfusion form similar to that of Gunz (1946), giving name, age, sex, diagnosis, history of previous transfusion, pregnancy, and stillbirths or jaundiced infants, was introduced, making it easy to select for special care those patients who may react badly to transfusion—those who have had previous transfusions, abortions, or miscarriages, or who have hæmolytic anæmia, collagen disease, or toxæmia of pregnancy. *Blood was promised* within twenty to thirty minutes of receipt of the recipient's blood, provided that, if any unusual reaction developed, the blood-transfusion would be delayed until the cause was known and a satisfactory cross-match obtained. During 1947 bovine albumin and anti-human globulin serum became available, and the capillary method of rhesus testing was proved, so that by 1948 the full rapid scheme could be operated. Even during 1947 blood had been made available at short notice, but routine rhesus testing had been confined to women under the age of 40.

Throughout this period each transfusion has bee reviewed by the laboratory staff, who seek evidence incompatibility. Every severe reaction to transfusion h been investigated.

Methods

ABO and D(Rh$_0$) homologous blood is normally used AB recipients receive AB, B, or A blood, but rarely bloo of group O. O rhesus-negative (cde/cde) blood is used "universal donor" blood only by the obstetric flyin squad.

ABO grouping was done by the tile method (Medic Research Council 1943; see also Allen et al. 1951) an rhesus grouping by the capillary method (Chown an Lewis 1946, 1951, Discombe and Meyer 1948). Cros matching was done on a slide as follows:

> Mix a large loopful of well-mixed donor's blood with tw or three drops of recipient's undiluted serum; rock at thirt second intervals for two minutes; *remove the fibrin networ* with a loop, and rock continuously for another minut examining by eye; then examine microscopically (× 100 tilting the slide to make the mixture run to and fro. Cov with a coverslip, and examine for rouleaux or agglutinatio (× 400); neglect pure rouleau formation, but, if agglutinate are present, transfer to an incubator at 37°C for five minute and re-examine.
>
> If the agglutinates have dispersed, the agglutination wa due to cold panagglutinins, which are quite common and ma cause a rigor if blood is used at refrigerator temperatur If agglutination persists, another bottle is tried, and th cross-match reinvestigated by the albumin or Coomb technique. False agglutination is usually caused by samplin the donor blood with a hot loop.

The success of this method depends on long enoug observation (three minutes or more) and *microscopical* observation. It is based on the old tile method used by Dr. H. F. Brewer for many years, and bears obvious similarities to the Diamond and Abelson test. It is also important to obtain a fresh sample of serum before each *transfusion of a series, for antibodies may* develop within a few days. Dr. A. E. Mourant (personal communication) has encountered a fatality caused by failure to take this precaution. If the anti-globulin technique is used, it is quicker and easier to sensitise and wash the cells in 3 in. × $^1/_2$ in. tubes than in precipitin tubes (as pointed out by Dunsford et al. 1950).

Results

Between December, 1946, and December, 1951, there were no fatal reactions. Seven ABO incompatibilities occurred, and one patient is known to have been accidentally sensitised to the rhesus factor. Two major reactions, one hæmolytic, had no discoverable cause. One patient who subsequently died was thought by the clinician to have received infected blood, a view I do not accept.

The incidence of known serological incompatibilities is therefore 1 in 1250 bottles transfused or about 1 in 550 transfusions. The mortality attributable to transfusion is not more than 1 in 10,000 bottles or 1 in 4000–4500 transfusions.

Case-histories

Two cases, 1 and 12, occurring before 1946, are added because of their general clinical interest.

ABO INCOMPATIBILITY

Case 1.—A man, aged 49, admitted on Sept. 18, 1945, with anæmia following melæna, had Hb 4·2 g. per 100 ml. Three bottles of group-B blood, slide cross-matched, were provided. There was a rigor after the contents of 2$^1/_2$ bottles had been transfused. Hb 6·55 g. per 100 ml. A second transfusion was requested. Group-B blood was found to be incompatible. The patient was re-tested and his blood was found to belong to group A. Before transfusion the anti-B-iso-*agglutinin* titre was 2 (macroscopic) and 8 (microscopic), rising to 125,000 (microscopic) on the tenth day.

Cause of Error.—A technician had misinterpreted the first grouping; a cross-match on a slide showed no agglutination macroscopically in ten minutes.

Case 2.—A man, aged 31, admitted on July 6, 1948, with næmia following hæmatemesis, had Hb 4·6 g. per 100 ml. nd blood-urea 250 mg. per 100 ml. He received 3 bottles of roup-O blood and then 150 ml. of group-A blood, when a vere rigor and hæmoglobinuria developed. Later he ceived 9 bottles of group-O blood.

Cause of Error.—Two bottles of blood had been taken ut of store for testing; these were group A, because e patient was confused with another of the same name. he technician was called away. When a messenger rrived from the ward, a student technician gave the ottles out without reference to anybody.

Case 3.—A woman, aged 56, was admitted on Oct. 1, 1949, ith recurrent hæmatemesis. Three bottles of group-O lood were cross-matched and placed in the laboratory refrigera-r. An hour later, after 250 ml. of blood had been transfused, rigor and hæmoglobinuria developed. Blood returned to the boratory belonged to group A.

Cause of Error.—Blood which had been cross-matched r a patient of the same name in a different ward was iven out by a clerk without reference to the technical taff.

Case 4.—A woman, aged 36, admitted at 5.30 A.M. on ct. 6, 1949, with ruptured tubal gestation, received 150 ml. f saline solution and $2^{1}/_{2}$ bottles of group-B blood during peration. At 8 A.M. she passed black urine; on being e-tested her blood was found to belong to group A. At 10 A.M. er urine was brown, and she received 80 ml. of 5% sodium icarbonate intravenously. At 2 P.M. her urine was normal in olour. Group-B cells were present in the circulation until ct. 10. The serum-bilirubin level was 3·2 mg. per 100 ml. fter transfusion, and 2·5 mg. per 100 ml. on Oct. 10; serum-otassium level, at 10 A.M. on Oct. 6, 97 mg. per 100 ml., r 24·7 m.eq. per litre; and anti-B-iso-agglutinin titre 256 efore transfusion, nil on Oct. 7, 8, and 9, rising to 4 on Oct. 10, nd 80,000 at room-temperature and 2,000,000 at 37°C on ct. 20.

Cause of Error.—A resident was harassed by a clinician or the blood, misinterpreted the grouping, and did not ait long enough over the direct match, which gave slow gglutination with small clumps.

Case 5.—A woman, aged 29, was admitted on Dec. 9, 949, bleeding from abortion. On Dec. 11 she received 1 ottle of group-A blood, which was followed by a rigor and æmoglobinuria. Later transfusion with compatible group-B lood was uneventful.

Cause of Error.—As in case 4. The blood should have een requested during normal working-hours, because he transfusion was not urgent.

Case 6.—A boy, aged 19, was admitted at 2.30 P.M. on an. 17, 1950, having cut his right ulnar artery. Operation was delayed because of a recent large meal. By 5 P.M. the oy's pulse-rate rose to 100, and his blood-pressure (B.P.) fell to 90 mm. Hg systolic. 250 ml. of group-A blood was given, which was followed by a rigor and fever. The B.P. rose to 120/70, and the patient improved and was operated on. Next morning he had severe abdominal pain, which persisted or two days, and hæmoglobinuria. There was no oliguria. The patient's blood was found to belong to group B.

Cause of Error.—As in cases 4 and 5.

Case 7.—A married woman had a severe postpartum hæmorrhage, and the flying squad was summoned. On their arrival her pulse was imperceptible, and a transfusion was started at once. After about five minutes, when $^{3}/_{4}$ of the bottle had been given, the doctor noticed that the blood that was being given belonged to group B and was rhesus-negative. He completed the transfusion. The patient had no reaction and recovered perfectly. Six weeks later her blood-group was found to be O, rhesus-positive, anti-A titre 1024, anti-B titre 256 at 20°C and at 37°C; hæmolysins against cells of groups A and B both of titre 2 were present.

Cause of Error.—An experienced sister had been given permission to take one bottle of group-O rhesus-negative blood from the store, should it be needed by the flying squad when the duty pathologist was not available. On this occasion she took rhesus-negative blood, but of group B. It is not wise to authorise any nurse to take blood from store; she may not realise that the ABO group is more important than the rhesus group.

Case 8.—A man, aged 67, underwent total gastrectomy with jejunal replacement for carcinoma, on Nov. 22, 1951. The œsophageal tube was removed too early and, on attempted replacement, coiled up; the œsophagus was distended with drip feed ('Casydrol' and milk) and leaked at the anastomosis, causing a subphrenic abscess. At 6.45 P.M. on Nov. 27, the patient underwent an operation for drainage and resuture: inhalation of contents of the œsophagus. He was given a transfusion of 1 bottle of group-A blood in the theatre, and $^{3}/_{4}$ bottle of group-B blood followed by 1 bottle of group-A blood in the ward; thereafter he received 1000 ml. of 0·85% sodium chloride in six hours and $1^{1}/_{2}$ litres of 10% dextrose containing 0·22% potassium chloride in nine hours. Catheterisation at 11.30 A.M. on Nov. 28 removed 30 fl. oz. of brown urine containing methæmoglobin, and at 5.30 P.M. 12 fl. oz. of orange urine containing only a trace of hæm pigment; thereafter the patient passed urine free from hæm pigments except on one occasion on Dec. 1. His inhalation pneumonia caused anxiety for some days, but he steadily improved and was allowed to sit out of bed on Dec. 3.

Cause of Error.—A nurse confused blood marked for – –LLAM with that marked for – –TTON, not noticing that one patient was in ward A3 and the other in A4. Errors of this sort should be avoided if blood is checked in the same way as are dangerous drugs.

UNCERTAIN CAUSE

Case 9.—A woman, aged 51, with group-B rhesus-positive blood, was given group-B rhesus-positive blood. After receiving 10–15 ml. she became flushed and lost consciousness; her pulse-rate was 120 and her pulse feeble. On recovery after eight hours, she was dazed, complained of pain in the back, and passed loose stools. She had no hæmoglobinuria.

Case 10.—A man, aged 75, with recurrent hæmatemesis, received 1 bottle of group-O blood; then the needle was thoroughly flushed with saline solution, and after twenty minutes a transfusion of homologous group-B blood was started. After 20 ml. had been transfused, a vigorous reaction developed. A Red Cross group-B donor was apparently compatible, but after 250 ml. a more violent reaction (fever, rigor, tachycardia, and hæmoglobinuria) developed. Group-O blood was transfused without incident.

In cases 8 and 9 no error in grouping could be discovered and no irregular antibodies could be detected by the indirect Coombs test.

Case 11.—A woman, aged 59, was admitted on Aug. 18, 1949, with subleukæmic chronic lymphatic leukæmia entering an acute phase; she was febrile. Blood-cultures on Aug. 26 and Sept. 5 were negative. On Sept. 6 she received 1500 ml. of compatible blood. On Sept. 8 she had sudden severe pain in both thighs; a blood-culture was positive for *Staphylococcus aureus*; and death took place at 2.30 A.M. on Sept. 9. At necropsy the liver was found to contain bacterial colonies without any cellular reaction.

Cause of Death.—Clinician's view: infected blood-transfusion. Pathologist's view: multiple emboli from a septic focus. The blood bottles had been returned to the depot before the blood-culture was found to be positive; so no definite conclusion could be reached.

Case 12.—A 5-gravida, aged 36, was admitted on June 10, 1946, with Hb 6·4 g. per 100 ml. in the 36th week of gestation; she had no signs of toxæmia. Her blood was group-O rhesus-positive. One bottle of group-O rhesus-positive blood was given without reaction; 250 ml. of group-O rhesus-negative blood caused a rigor, sweating, fever and a convulsion, then dyspnœa and abdominal pain. B.P. 74/34; pulse-rate 112; urine volume 20 ml., colour black. She was treated with intravenous fluids, and thirty-six hours later was delivered of a stillborn infant. Thereafter the B.P. fell, jaundice appeared, and she died fourteen hours after delivery, having passed small volumes of clear urine shortly before death. At necropsy the usual changes of incompatible transfusion were found.

Cause of death unknown. The coroner held that blood twenty-one days old was too stale for use. My view is that an anti-c, anti-Duffy, or anti-Kell agglutinin might have been the cause, or the blood might have been overheated, though there was only 0·5% free Hb in the plasma.

Case 13.—Inadvertent immunisation to the rhesus factor took place in one patient for whom a capillary test was set up in a tube of more than 1 mm. bore; the observer mistook the eddies which occur during mixing for a positive reaction, and issued rhesus-positive blood. Fifteen minutes later the reaction was clearly negative, but by then the transfusion had been started.

Discussion

Gross blunders, either administrative (cases 2, 3, 7, and 8) or technical (cases 1, 4, 5, 6, and 13) are the common causes of error; and the technical errors are usually due to haste, often needless. Administrative errors are eliminated by proper organisation, technical errors by reducing the need for haste, as by encouraging the use of small-pool plasma or dextran. Two cases are of quite unknown cause in spite of full reinvestigation. The one fatal case certainly attributable to transfusion occurred before modern techniques were available, but the consensus of opinion is that it was caused by overheating the blood.

This is not, by ordinary standards, a bad transfusion record, for Wiener (1943) cites 9 deaths in 8236 transfusions. Nicholson (1948), however, reports from a group of blood-banks 67,844 transfusions with but 18 hæmolytic reactions and 3 deaths, and states that the usual causes of accidents are erroneous labelling of blood samples and similarity in patients' names (cf. cases 2, 3, and 8).

Dahr (1950–51 and personal communication) has reviewed 26 ABO incompatibilities with 4 deaths, and 25 rhesus incompatibilities with 7 deaths; an incomplete survey of the literature, excluding single cases, raises this to 33 ABO with 7 deaths and 33 rhesus with 10 deaths. There are two types of clinical response to incompatible transfusion. One is immediate circulatory collapse ("shock") (cases 9 and 11), which carries a very high mortality; Dahr found 5 deaths among 8 cases of this type, and Nicholson's 2 fatal cases were similar. The ordinary hæmolytic reaction, with pain in the loin, rigor, fever, and hæmoglobinuria, sometimes followed by anuria, is less lethal; Dahr reports 16 cases with 3 deaths, and the 7 cases reported here suffered little inconvenience.

It is remarkable that no patient developed anuria. Possibly this excellent record is due to the expectant treatment employed after transfusion accidents. I have seen a few patients treated actively by forcing fluids and administering sodium sulphate intravenously, and they all developed anuria and died. Even when anuria does develop, the Borst (1948) régime (Bull et al. 1949) should permit recovery in about 90% of patients.

Circulatory collapse seems to be commoner with rhesus incompatibility, possibly because of the extraordinary lability of the vascular system during late pregnancy and toxæmia of pregnancy (case 11, Doniach and Walker 1946, Young 1942).

Since the ultimate criterion of success in blood-transfusion is the patient's survival, these accidents are not important, except that they show very clearly how incompatible transfusions are caused; they may result from bad administration or unskilful technique.

Administration is unsatisfactory if responsibility for the entire process of blood collecting, grouping, and issue to the wards is not centred in one man. If responsibility is divided, it becomes impossible to find the cause of errors.

Administration is unsatisfactory if too many people are allowed to handle blood; there is rarely any need for more than four or five to do so—the director, his registrar, the blood-grouping technician and his deputy, and the resident pathologist when on duty. No clinician should be expected to leave an ill patient to go and select blood for transfusion. It is desirable that requests for blood be sent to the laboratory individually, by special messenger, and not collected with the ordinary pathological specimens.

Technical errors can be avoided by appointing a specialist blood-grouping technician to work in close association with the director and the registrar. If the technician asks advice, it must be given *at once.* Residents must not be harassed by their clinical colleagues, and this can be minimised, though not prevented, by encouraging the use of small-pool plasma or dextran. Undergraduate training should emphasise not only the life-saving powers of blood-transfusion but also its dangers, and special emphasis must be laid on the fact *that the immediate treatment of acute hæmorrhage is to* replace the blood lost by *any* fluid which will remain within the vascular system for ten hours or more without causing harm. This holds even if half the blood volume is suddenly lost by a previously healthy patient; replacement by small-pool plasma or dextran will restore the blood volume, and if blood is not immediately available small-pool plasma or dextran must be used. Restoration of the blood volume is *the essential part of the treatment* of sudden hæmorrhage. If blood can be made available to restore hæmoglobin as well, so much the better; but *emergency transfusion is far less necessary now than it was in 1946.*

Nurses are usually taught that blood should be warmed before administration: they are not taught that it becomes lethal if subjected to a temperature greater than that of the body. They therefore do not use a thermometer to check the temperature of the water in which the blood is to be warmed, and some of my colleagues have been offered water at 130°F (55°C) in which to warm blood. Baker (1937) records the case of a patient killed in this way (see also Drummond 1949). Blood causes no harm if given at refrigerator temperature; and venous spasm and rigors due to cold agglutinins can be prevented by standing the bottle in a warm room for an hour before administration. If blood must be warmed it should be warmed in the laboratory or in a thermostatically controlled jacket such as that made for us by Thermega Ltd.

Frozen blood is equally dangerous. We have to allow blood for drip transfusions to be kept in the ward. On one occasion 2 bottles were returned frozen solid, because a nurse had wanted to keep some ice-cream and had altered the refrigerator thermostat. The group engineer has now locked the controls of half the ward refrigerators to 35°–39°F and marked these in red "Suitable for the storage of blood," leaving the others, marked in black "Not to be used for storing blood," for ice-cream preservation and other culinary functions. Even so, an associated hospital froze its emergency stock when the thermostat broke down; and during a severe winter we had to put an electric hotplate in our own refrigerator, which is in an unheated outhouse.

Fortunately, frozen blood, even when thawed, looks different from unfrozen blood; but a busy and agitated house-officer might not notice the difference, and Drummond (1949) records a case in which frozen blood was deliberately thawed and administered.

Conclusion

The technique described above is satisfactory in that it permits transfusion at very short notice without causing deaths from incompatibility.

The introduction of small-pool plasma, and more recently of dextran, make emergency transfusions of blood less necessary.

Perhaps the free use of small-pool plasma or dextran will make it possible to adopt a more satisfactory method for cross-matching. Were it possible to use the anti-globulin method for every case, the only incompatibilities likely to occur would be those due to inaccurate labelling of specimens, confusion between patients of similar names, and overheating and freezing of blood.

Summary

6 ABO incompatibilities without a death, and several other transfusion incompatibilities, occurring during the transfusion of over 10,000 bottles, are described.

Methods which have enabled compatible blood to be issued within thirty minutes are described.

The chief causes of error are haste, and confusion between patients with similar names.

The dangers of overheating and overcooling blood are emphasised.

The advantages of using small-pool plasma or 'Dextran' to restore blood volume are emphasised.

I am indebted to many members of our medical and technical staff for their help during the past five years, particularly to Mrs. H. Meyer, senior technician for blood-transfusion, and to Dr. H. B. W. Greig, registrar since 1950. I am indebted also to Dr. W. d'A. Maycock, Dr. A. E. Mourant, and Dr. D. M. Parkin, who have read successive drafts of this paper and given me the most valuable criticism and advice.

REFERENCES

Allen, F. H. jun., Diamond, L. K., Madden, H. J. (1951) *New Engl. J. Med.* 244, 925.
Baker, S. L. (1937) *Lancet*, i, 1390.
Borst, J. G. G. (1948) *Ibid*, i, 824.
Bull, G. M., Joekes, A. M., Lowe, K. G. (1949) *Ibid*, ii, 229.
Chown, B., Lewis, M. (1946) *Canad. med. Ass. J.* 55, 66.
— — (1951) *J. clin. Path.* 4, 464.
Dahr, P. (1950–51) *Langenbecks Arch. klin. Chir.* 266, 82.
Discombe, G., Meyer, H. (1948) *J. clin. Path.* 1, 73.
Doniach, I., Walker, A. H. C. (1946) *J. Obstet. Gynæc.* 53, 140.
Drummond, R. (1949) *Med. Pr.* 222, 325.
Dunsford, I., Cowan, J., Malone, R. H. (1950) The Coombs Test. Sheffield.
Gunz, F. W. (1946) *Brit. med. J.* i, 601.
Lehane, D., Kwantes, C. M. S., Upward, M. G., Thomson, D. R. (1949) *Ibid*, ii, 572.
Medical Research Council (1943) *Med. Res. Coun. War Memo.* no. 9.
Nicholson, M. J. (1948) *Anæsthesiology*, 9, 345.
Race, R. R., Sanger, R. (1950) Blood Groups in Man. Oxford.
Wiener, A. S. (1943) Blood Groups and Transfusion. 3rd ed., Springfield, Ill.
Young, J. (1942) *Brit. med. J.* ii, 715.

EFFECT OF ADRENOCORTICOTROPIC HORMONE ON THE SURVIVAL OF HOMOGRAFTS

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THIS paper reports our experiences with skin grafts implanted in three patients receiving adrenocorticotropic hormone (A.C.T.H.).

When skin is transferred from one person to another, the graft is called a homograft; when the skin is grafted elsewhere in the same individual, the graft is called an autograft. Almost all observations of homografts, both in man and animals (Medawar 1944), indicate that they do not survive permanently. Thus Longmire et al. (1947) report that when 71 homografts from unrelated donors were implanted in a child with severe burns, they all disintegrated and were absorbed in 8 weeks. Medawar (1946a and b) suggested that such grafts disintegrate because the host forms antibodies to the foreign proteins they contain; but until some system of skin-typing, analogous to blood-typing, is devised, this hypothesis must remain untested. Certainly, it would explain the shorter survival of any later implantations of homografts (Medawar 1944), and the report of survival of homografts in identical twins (Brown 1937). Also it might explain the survival for 2 years of a transplant from parent to son (Kearns and Reid 1949). On the other hand, some skin elements of a homograft from an unrelated donor have survived for 6 months (Blocker 1951), an observation which raises a question about which we have found no published details—namely, the statistical chances of especial longevity of homografts in humans.

If burns are shallow and can be kept free from infection (Colebrook 1950) they should not need grafting; if they are deep but small there will be no difficulty in finding donor sites. But if they are both deep and extensive autografts may not easily be provided. The rationale of using homografts may be summarised as follows:

(1) "The nearest approach to the ideal dressing for severely burned skin is a healthy split-skin graft, autogenous or homologous" (Saunders and Moore 1950).

(2) Covering the burned area with skin excludes infection from the granulations.

(3) Covering with skin, including homografts, seems to reduce the constitutional effects of severe burns—e.g., pain, anæmia, and poor nutrition. This effect may even be life-saving (Brown 1937).

(4) While homografts survive, such areas of skin as remain to act as donor sites can be stripped of split-skin grafts at intervals of 2–3 weeks; such grafting operations are performed in a relatively fit patient, and the skin obtained is ready for application as homografts disintegrate.

The use of A.C.T.H. and cortisone has been found to alter antigen-antibody relationships (Finland et al. 1950, Soffer et al. 1950), and Mote (1950) suggested that such alterations might permit the permanent survival of homografts. While our own investigations into this possibility were in progress Whitelaw (1951) reported a case of "permanent" survival of homografts under A.C.T.H. therapy. But it must be stated at the outset that our findings have proved discouraging; they confirm the negative results of other investigators using cortisone or A.C.T.H. for long periods (Ellison et al. 1952, Cannon et al. 1952, Mulholland 1951, Longmire 1951), A.C.T.H. for a short period in humans (Baxter et al. 1951) and cortisone in animals (Billingham et al. 1951).

METHODS OF INVESTIGATION

We were careful to consider six important aspects in planning these observations.

(1) It was important that the burns to be homografted were of such size that they could not heal over from the edges; it has been stated that skin can grow out some 2 cm. from the edge of a deep burn (Trueta 1943). (2) In so far as homografting would be of greatest value in extensive burns, we decided that a study of homografts to the trunk and thigh areas would be most profitable, because unless these areas are burned, the surgeon has adequate donor sites for autografting. (3) It was important to be sure that our cases had undoubted third-degree burns, otherwise we might mistake the patient's own healing skin for surviving homografts. (4) We were careful to avoid giving A.C.T.H. before the depth of burn could be diagnosed, for we did not know how A.C.T.H. might alter the criteria for the clinical diagnosis of depth of burning. (5) Furthermore, in our state of ignorance of the factors which might or might not influence survival of homografts, it was clearly imperative to disperse them in a random fashion wherever possible, and to include samples of the patient's skin, to ensure that failure of homografts was not to be explained by some unknown cause. (This precaution proved impossible in one case.) (6) It also seemed essential to ensure that the A.C.T.H. was in fact stimulating the patient's adrenal glands; otherwise failure of the homografts might be due to a lack of cortical hormones in the blood, which would thus invalidate the experiment. We were aware of this possibility because we have previously found inadequate adrenocortical reserve in burned patients during their convalescence.

Accordingly, we selected three patients with extensive burns, undoubtedly third-degree, involving trunk and thighs—an adult male, an adult female, and a female child. None had been treated previously with either A.C.T.H. or adrenocortical hormone, and all had adequate adrenocortical reserves (Thorn et al. 1948). The homografts were implanted, and were examined and photographed whenever dressed. Bacteriological cultures were taken whenever the burns were dressed or at convenient intervals when the grafts were left open to the air. The adrenocortical function in each case was assessed by various laboratory investigations, and by clinical observation. In the adults, we were able to study the following:

(1) The eosinophil-count by the method of Randolph (1944), taking care to count 1 c.mm. of blood, to reduce statistical sampling errors.

(2) The urinary excretion of formaldehydrogenic corticosteroids daily, or over a period of days, by the method of Corcoran and Page (1948).

(3) The 17-ketosteroid excretion by Tompsett's method (1949).

(4) The sodium and potassium balances between oral and intravenous intake and urinary excretion.

(5) Glycosuria, when it occurred.

It was not possible to maintain all these laboratory investigations in the child.

CASE-REPORTS AND INVESTIGATIONS

Case 1.—A coloured woman, aged 24, was burned over her abdomen, thigh, arms, and back, when her housecoat caught fire on Oct. 13, 1950. She was admitted to hospital and resuscitated. Her burns were diagnosed as third-degree, and by Oct. 25 were infected. She was admitted to our burns unit on Oct. 30.

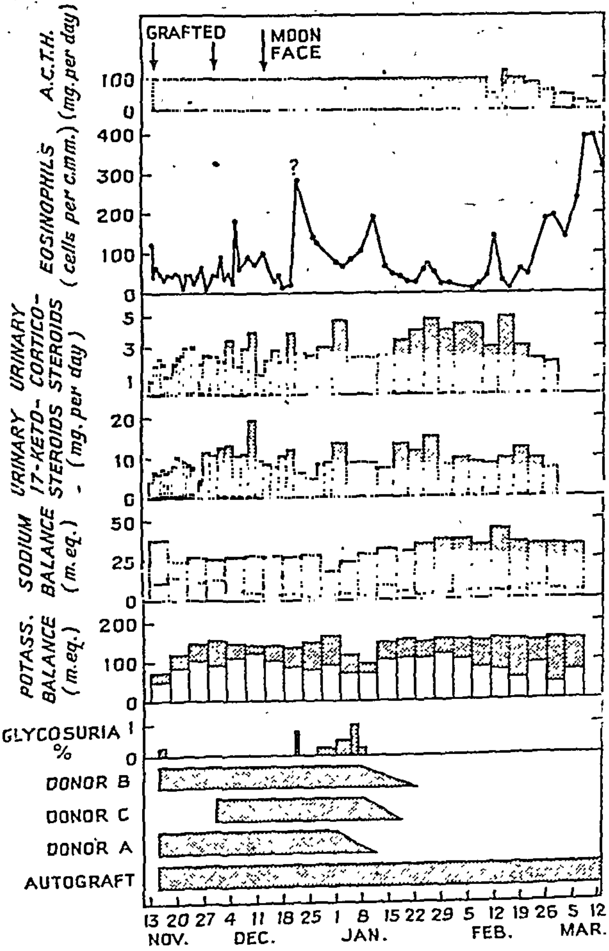

Fig. 1—Results in case 1, a woman, aged 24, with 54% third-degree burns of abdomen, back, thighs, and arms.

She was a quiet, well-developed, but undernourished woman who had grossly infected deep burns, involving 45% of her body-surface. Cultures grew *Proteus vulgaris*. The burns on her abdomen, back, and arms showed no islets of epithelium, the areas being covered with pink, rather œdematous, granulations.

It was decided to try homografting and A.C.T.H., 100 mg. of which was given daily from Nov. 14.

Split-skin grafts were obtained from two donors on Nov. 15, one was the patient's husband (A) and the other was unrelated (B). These grafts were stored overnight at 5°C. On Nov. 16, three 4 in. square split-skin grafts were taken from the patient, and, with three of the same size from each of the donors, they were laid out on the remarkably clean and dry granulations found over abdomen. They were arranged in a 3 × 3 latin square, derived from statistical tables (Fisher and Yates 1949). The patient's clinical condition dictated that the remaining homografts were placed over the arms, thighs, and elsewhere about her trunk and back. All areas were covered with dressings.

Adrenocortical Response.—All the laboratory tests for adrenocortical function indicated adequate response to A.C.T.H. during the study period and after 1 month the patient had a moon face. Her general condition seemed to improve and although she had periods of mental disorientation with euphoria, she gained weight and the infection of her burns seemed to regress, although swabs invariably grew *Proteus vulgaris*.

Fate of Grafts.—All the grafts in the latin square layout on the abdomen took, and so did 90% of the other homografts. After 28 days the grafts and donor sites were all in excellent condition and there was complete bridging of the 1 in. gaps between grafts on the abdomen. The patient's back was macerated and skin from another unrelated donor (C) had to be implanted there. The arms were left exposed at this time. Within another week, the homografts from donor A on the arms began to show flaking, leaving reddish-brown, though dry, areas. 6 weeks after their application, two of the three grafts on the abdomen from donor A, which had previously appeared stable, showed evidence of dissolution with thin, skin blisters, many of which ulcerated. The patient's own skin grafts, and those of donor B were intact and firmly healed. At the 7th week, all homografts to the arms were macerated, and all skin from donor A on the abdomen had degenerated and was absorbed leaving clean granulations. At that time the grafts from donors B and C on abdomen and back respectively were still intact; but in the 9th week they showed surface flaking and broke down and were absorbed over the following 2 weeks. The patient's own skin grafts were firmly healed.

During these 11 weeks, skin grafts which had been taken on several occasions from the patient, were laid down as and where the homografts disintegrated. Unfortunately, after prolonged A.C.T.H. therapy, the take of autografts was not good; only 25% of those applied in the 9th week after the start of A.C.T.H. therapy took and further implantations had to be made to some areas of the arms, abdomen, and back. Furthermore, the granulation tissue over the arms grew high despite A.C.T.H., and by the 8th week there was a very poor range of movement at both elbows. This was contrary to expectations; and it is regretfully admitted that these joints have had to be manipulated, all other physiotherapeutic attempts to improve the range of movement having failed.

One other problem arose after the final dissolution of the original homografts. When A.C.T.H. dosage was reduced the patient developed a high fever (103°F) and fast pulse, and it was necessary to return to 100 mg. A.C.T.H., augmented by 12·5 mg. intravenously, before the fever settled. The dosage was then brought down very slowly and the last dose was given on March 13. Towards the end of this course the only areas unhealed by split-skin grafts taken from the patient herself were on the abdomen, and these small areas were later grafted and healed.

The results in this case are shown in fig. 1. Sodium and potassium balances are plotted for periods of 5 days; average daily intake is measured from the base-line to the top of the shaded area and average daily excretion from the base-line to the bottom of the shaded area. Thus the shaded area represents the excess of intake over output. The sloping part of the homograft blocks represent the period of their disintegration.

Case 2.—A white man, aged 41, was admitted to the burns unit on Nov. 26, 1950, after his clothes caught fire. His limbs were cold; the pulse-rate was 110, respiration-rate 24, and blood-pressure 90/60 mm. Hg. The skin over the chest, back, buttocks, and both thighs, involving 32% of his body-surface, was scorched and blackened. He was resuscitated with 'Dextran,' glucose, electrolytes (7400 ml. in all) intravenously over the first two days. His burns were dressed and his recovery from shock was uneventful. On Dec. 20, he was taken to the operating-theatre, and the sloughs were excised from most of his burned areas, leaving clean granulations with no evidence of islets of epithelium. This operation necessitated transfusion with 1500 ml. of blood. With burns of this extent and presumed depth, and in the absence of large donor areas over trunk or thighs, this patient was a suitable case for homografting under A.C.T.H. therapy.

On Dec. 28 homografts were taken from two of the patient's brothers (D and E). On Dec. 29 3 in. square autografts were cut from the patient's left thigh under local anæsthesia and implanted on the burns over the lower chest, left groin, and right groin and thigh. The 3 in. square homografts from D were placed over the remainder of the burned areas on the chest, while those from E, also 3 in. squares, were placed over the abdomen below the umbilicus. This layout was designed to space the homografts so that there could be no question of healing by growth from the edges. The grafted areas were dressed with occlusive bandages. A.C.T.H. 25 mg. every 6 hours, was started immediately after the operation.

Adrenocortical Response.—The patient felt much better on A.C.T.H., and all laboratory tests indicated an excellent adrenal response. Within 2–3 weeks he had a moon face, and after 8 weeks he had a humped back. His condition demanded a high-calorie diet and he was given 400 g. carbohydrate and 4000 calories daily. Glycosuria, which was observed before A.C.T.H. began, was controlled by 100 units insulin daily, but returned whenever the patient was operated upon.

During the course he had periods of mental disorientation and was frequently irrational. The excretion of formaldehydrogenic corticosteroids was abnormally high. Also, the patient had intermittent jaundice from Dec. 5, 1950, until his death on March 19, 1951.

Fate of Grafts.—The homografts implanted showed a 95% take; the autografts in the groin were rubbed off by the dressing, but the remainder on the chest and right thigh took completely.

2 weeks after the original implant, further 3 in. square homografts from D were placed over the back. At this time all the original grafts had grown $^1/_2$ in. from their edges. A week later the first homografts and autografts were growing well, and the homografts to the back showed a 90% take. There was such good healing of the burns of the trunk that no dressings were needed. Autografts were applied to various uncovered areas of the thighs at this time; and they took well.

After 6 weeks, the autografts and the homografts from D above the umbilicus were healthy, but the homografts from E to the lower abdomen were red and covered with flakes of keratin. Autografts implanted to the left thigh in the 7th week took poorly (5%). On March 2, 1951, the homografts from E were sloughing; those from D were still intact. By March 6 the E homografts had sloughed and the area was covered with pus (swabs grew *Proteus vulgaris* and *Pseudomonas pyocyanea*). Autografts were implanted on this area and on the trunk, and covered with an occlusive dressing. On March 16, 11 weeks after their implantation, the homografts from D on the upper chest were cyanotic and showed flaking keratin over their surfaces. The patient's donor sites over the shoulders were deeply ulcerated and infected. The wounds were covered with 'Furacin' gauze and an occlusive dressing.

Termination of Illness.—We decided to reduce the A.C.T.H. dosage because the patient was becoming more confused mentally and also because of the state of his donor sites. On March 17, 79 days after the start of the trial, the dosage was reduced to 20 mg. every 6 hours. Next day the patient was febrile (rectal temperature 103°F) and mentally disorientated in time and space. The lower abdomen was covered with purulent material; the burns were re-dressed and intensive antibiotic therapy begun. He became extremely ill and dehydrated. 1000 ml. of 5% dextrose in water was given intravenously, but he died on March 19. This case is summarised in fig. 2.

Necropsy (Dr. G. R. Hennigar and Dr. J. Kirk).—The adrenal cortices were hypertrophied in the zona fasciculata with atrophy of lymphocytic tissue. The pituitary body showed hyaline changes in the basophils and the liver, diffuse and central fatty infiltrations with minimal focal necrosis. The kidneys revealed fibroid thrombi in the glomerular tufts, and acute pyelonephritis with necrotising papillitis. Sections of the skin from the area homografted on the chest showed spotty epithelialisation with thin epithelium and a poorly defined basal layer and stratum granulosum. No skin appendages were seen in sections from this area; there was lymphocytic infiltration around vessels. (Similar findings have been reported in biopsies of homografts, Ellison et al. 1952.) Below the skin grafts there was considerable hyalinised connective tissue with inflammatory reaction. There was no single major cause of death.

In the third case we were unable to estimate the steroid excretion and we decided to assess adrenocortical function by following the eosinophil-count and the urinary excretion of sodium and potassium. Unfortunately, these latter determinations also proved impossible for long because of diarrhœa and contamination of the urine samples by fæces. Since the other cases had had high steroid excretions and there remained a possibility that overstimulation of the adrenal cortex might have been responsible for the failure of homografts, this patient was maintained on a lower dosage of A.C.T.H., 50 mg. instead of 100 mg. per day, starting 9 days before the implantation of the homografts.

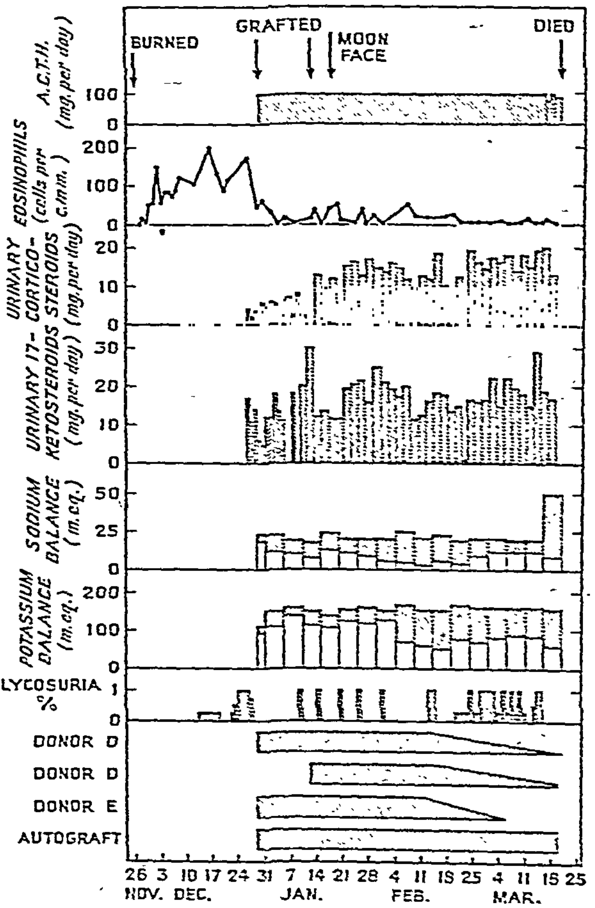

Fig. 2—Results in case 2, a man, aged 41, with 32% third-degree burns of abdomen, back, thighs, &c.

Case 3.—A coloured child, aged 5, was admitted to hospital on Dec. 2, 1950. She had deep and extensive burns of the back and abdomen, the right thigh, and the inner aspect of both arms, involving 36% of her body-surface. Resuscitation was started and over the next 24 hours she received 5220 ml. of fluid, including 2000 ml. of dextran, 500 ml. of blood, and 1250 ml. of Ringer's solution intravenously on the first day, and 1785 ml. of fluids on the second day. Her condition remained satisfactory during the shock phase.

For 5 days she ran a hectic course, attributed to infection of her burn. Her temperature rose to 105°F and her pulse-rate on one occasion to 156. She was given large doses of antibiotics, and by the 20th day she was fit for her first grafting procedure. Autografts were cut from the right thigh and placed over the upper abdomen and chest. 80% of these grafts were found to have taken 7 days later. However, the patient's back was in unsatisfactory condition; and cultures grew *Bacterium coli* and *Bact. aerogenes*, sensitive to penicillin, streptomycin, and aureomycin, which were administered. By Jan. 4, 1951, 33 days after admission, the sloughs from the burns on the back had separated well, leaving moist granulations.

Homografting under A.C.T.H. was decided upon because the only reasonable donor site on her left thigh had been used for the grafts to her abdomen and there appeared to be a great risk of infection unless the granulating surface on her back was covered. On Jan. 6 A.C.T.H. was started (50 mg. per day), and 5 days later homografts were applied to the back. The skin from one donor (F) was spread over an 8 in. square in the mid-lumbar region. The remaining skin from donor G was placed as postage-stamp grafts over the rest of the back around the central area.

Adrenocortical Response.—The eosinophil-count fell promptly after the administration of A.C.T.H., and after 5 weeks she had a moon face with growth of hair on the cheeks and forehead. Changes in the sodium and potassium balances, while detectable by analysis of the urine, were not nearly as marked as in the two previous cases.

Fate of Grafts.—After 17 days the homografts were found to have taken so well that dressings were not needed. After 23 days it was observed that the outer layers of the homografts from G were beginning to separate. By Feb. 10, 30 days after implantation, the homografts were in poor condition and showed signs of sloughing, especially those from G. The patient's back was grossly infected with a considerable amount of pus where the homografts were degenerating. Cultures grew *Proteus vulgaris. Ps. aeruginosa*, and *Staphylococcus aureus.* All these organisms were sensitive to penicillin, which was administered. By Feb. 16, all the grafts from G had degenerated and sloughed off. The grafts from F were still intact but appeared unhealthy and cyanotic with flaking of the superficial epithelium.

Homografts from F continued to degenerate slowly over the following 15 days and all had sloughed by March 2, 51 days after implantation. A.C.T.H. dosage was gradually lowered and autografts were applied to the unhealed areas over the back, which now showed high, dry granulations; 40% of the grafts were successful. A.C.T.H. was finally stopped on March 12 (fig. 3).

Subsequent healing was slow and repeated grafting was necessary. She was eventually discharged on May 7, 1951.

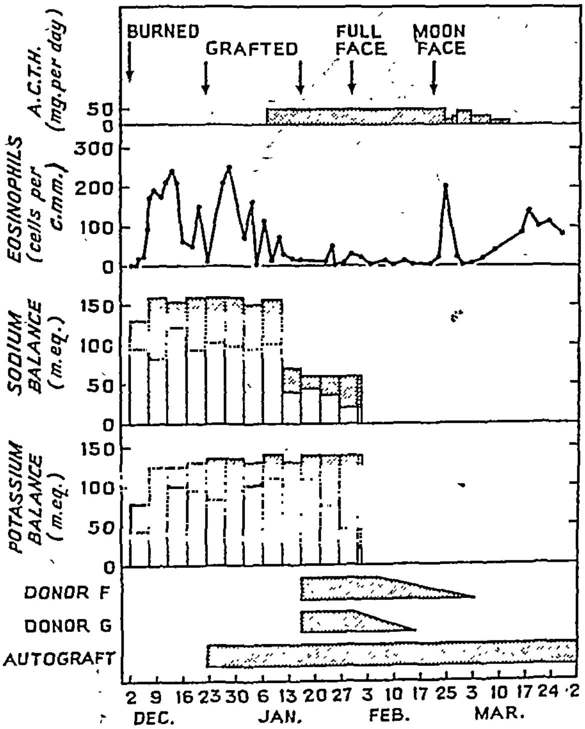

Fig. 3—Results in case 3, a girl, aged 5, with 36% third-degree burns of abdomen, back, and right thigh.

DISCUSSION

In this trial, autografts survived but homografts degenerated. These results are at variance with those reported by Whitelaw (1951), and we must examine any differences which might be responsible. We took considerable care to ensure that all the burns studied in our series had destroyed the whole thickness of the skin. The diagnosis of deep burns in the case reported by Whitelaw rests upon the absence of islets of epithelium 35 days after what was believed to be deep burning, *during which time* the patient was receiving A.C.T.H. We are therefore forced to suggest that A.C.T.H. may so alter the normal healing of shallow burns as to conceal the re-growth of islets of epithelium for long periods.

A second difference is our use of postage-stamp or larger grafts, whereas Whitelaw used pinch grafts. It may be, therefore, that A.C.T.H. does maintain the growth of homografts when they are of pinch-graft size, possibly because the total dose of antigen is less than in our cases. The skin which grows from such small homografts, being constituted, presumably, of the host protein, may not undergo degeneration as a result of any antibody action; this point warrants further study. Finally, the case reported by Whitelaw was a flash-burn, whereas our cases were all flame burns. There might be some variation in the pathological physiology of these two sorts of burns such that A.C.T.H. has some influence on the course of the former but not of the latter.

Depth of Burning

When homografts fail, as in this trial, it is not nearly so important to know the exact depth of burning as it is when homografts are claimed to have survived permanently. Clinically all three cases ran a course typical of whole-skin thickness burning; after the sloughs separated they left granulating areas free from islets of host epithelium. Moreover this diagnosis was supported by the fact that the autografts did not leave healing epithelium below. In case 2 some homografts had not completely degenerated at the time of death, but no deep skin elements were found in sections taken from these areas.

Response to A.C.T.H.

We were anxious to be sure that any failure of homografts could not be attributed to inadequate adrenocortical response to A.C.T.H. All three cases developed moon faces, and case 2 developed the humped back usually associated with hyperactivity of the adrenal cortex.

Case 1 showed depression of the eosinophil-count, over-excretion of formaldehydogenic corticosteroids and 17-ketosteroids, depression of urinary sodium excretion, and elevation of urinary potassium excretion. She also developed glycosuria. Other tests not reported here demonstrated that she had an insulin-resistant glucose tolerance, which has been reported in Cushing's disease (Himsworth and Kerr 1939). Further, these abnormalities disappeared when A.C.T.H. was stopped. We concluded on this evidence that the adrenal cortex was adequately stimulated.

Case 2 had similar laboratory findings and also developed an insulin-resistant glucose tolerance. Laboratory tests,

ATTEMPT TO RELATE ADRENOCORTICAL RESPONSE TO SURVIVAL OF HOMOGRAFTS

	Case 2	Case 1	Case 3
A.C.T.H. dosage	100 mg. per day	100 mg. per day	50 mg. per day
Sodium retention	+ +	+ + +	+
Potassium excretion	+ + +	+ +	+
Depression of eosinophils ..	+ + +	+	+ +
Mean daily urinary "free" corticosteroid excretion ..	13 mg.	3·3 mg.	?
Mean daily urinary 17-ketosteroid excretion	17 mg.	9·7 mg.	?
Survival of homografts (days)	80 + (D) 66 + (D) 67 + (E)	53 (A) 68 (B) 50 (C)	47(F) 31(G)
Probable order of magnitude of response	1	2	3

especially those measuring urinary excretions of steroids, reflected more intense activity than in the other cases. He also developed a moon face most quickly, making it reasonable to suggest that the increase in urinary steroids indicated high adrenocortical activity.

Case 3 received a lower dosage of A.C.T.H. and did not show very profound alterations in sodium or potassium excretion. However, since the eosinophil-count was depressed, and she developed clinical signs of Cushing's disease, we are confident that there was increased adrenocortical activity.

Homograft Survival

The survival of homografts was unusually long in cases 1 and 2, though it is not certain that these results are statistically significant. The homografts did not survive permanently in cases 1 and 3, and those from donor C had perished before case 2 died. It is impossible, therefore, to be certain that the D homografts in case 2 would have survived had the patient lived. We are inclined to believe that they would not have survived, because sections taken from these homografts after death showed a very thin epithelium with no well-formed rete pegs. Ellison et al. (1952) regarded the absence of rete pegs as diagnostic of impending disintegration.

Relation between Response and Survival

Though none of the clinical findings or laboratory tests give an absolute, quantitative measure of adrenal function, an attempt has been made in the table to grade the three cases according to adrenocortical response. There is some evidence that the duration of survival of homografts may be related to the intensity of the adrenocortical activity in the host. A similar relation between duration of survival of homografts and the dose of 'Cortone' in rabbits has been noted by Sparrow (1951). Each case required blood-transfusion before the investigation began. Only patient no. 2, whose homografts survived longest, was transfused during the study period. Animal investigations suggest that blood-transfusions do not greatly alter the time of survival of homografts (Medawar 1946b). We do not, therefore. believe that this transfusion in case 2 invalidates our tentative conclusion relating homograft survival to intensity of adrenocortical activity.

Reports of the failure of wound healing and the development of bed-sores with A.C.T.H. naturally raised the question whether the adrenocortical activity induced had been too great for the survival of homografts. We do not think so, (1) because the results in the table suggest, if anything, the opposite state of affairs; (2) because both the homografts and autografts took and grew well; and (3) because the autografts survived, whereas the homografts failed.

Complications of A.C.T.H. Therapy

Cases 1 and 2 both had periods of mental disorientation, and both developed a diabetic state. The granulations over the burned areas grew high in cases 1 and 3, so high that case 1 needed manipulation of the elbows and case 3 required excision of scar tissue and grafting. Furthermore, in every case, subsequent implantations of autografts were difficult because of the low proportion of such grafts which took and continued to grow.

It is generally recognised that the proportion of autografts which take tends to fall during the convalescence of any burned patient. In cases not treated with adrenal hormones or A.C.T.H., this might be attributed to diminishing adrenocortical function. Be that as it may, our results show that it would be unwise to expect universal improvement in the percentage take of autografts from intense stimulation of the adrenal cortex in the late convalescence of burns. If faulty action of the adrenal cortex is a cause of failure of grafts, the necessary balancing of adrenocortical function from case to case may prove an exacting task.

Despite reports that A.C.T.H. prevents the clinical signs of infection, we observed pus in all three cases. It should be remarked that infection appeared in the test homograft sites *after* these regions began to break down. In every case the homografts grew to bridge the intervening granulations well enough to close the wound and exclude infection. Thus, we do not believe that infection, per se, can be the cause of failure, especially as the autografts survived.

In cases 1 and 2 the reduction of A.C.T.H. dosage heralded complications and the patients became febrile. In so far as A.C.T.H. and cortisone seemed to prevent the localisation of infection and also to alter the usual systemic response to infection, these febrile episodes may have been caused by a sensitivity to invasive infection, which may have been masked during A.C.T.H. therapy.

CONCLUSIONS

It is our conclusion that A.C.T.H. prolongs, but does not perpetuate, the survival of homografts on deep flame burns, and that early skin closure is just as urgent as it was before the discovery of this hormone.

SUMMARY

The effect of A.C.T.H. upon the survival of homografts has been studied in three cases of burns involving the whole thickness of the skin. In each there was evidence of good adrenocortical response and in two cases the homografts survived for an unusually long time. However, they all degenerated in the end and showed no sign of permanent survival. The length of survival seemed to be related to the intensity of adrenocortical response.

A.C.T.H. did not prevent bacterial invasion or the clinical signs of infection in these burns. High granulations grew over burned areas despite A.C.T.H. therapy. A.C.T.H. did not increase the percentage take of delayed autografts. Various complications of A.C.T.H., including glycosuria and mental disorientation, were encountered.

It is a pleasure to acknowledge the clinical assistance of our colleagues, Dr. P. W. Robinette and Dr. E. M. Rice, the technical assistance of Miss Carolyn Martin, Miss Elizabeth Hubbard, and Miss Lucy Harvie, and the special help of Dr. S. M. Levenson, Miss E. Lounds, and Miss M. Robinson of the U.S. Army medical nutritional laboratory, who were responsible for controlling the diets in these patients. We also wish to thank Dr. J. R. Mote, for providing the A.C.T.H. (Armour), and the Medical Research Council for assistance to one of us (W. J. H. B.). Our work was made possible by the coöperation of the department of the U.S. Army, Office of the surgeon-general, and the Office of Naval Research.

REFERENCES

Baxter, H., Schiller, C., Whiteside, J. H. (1951) *Plastic Reconstruc. Surg.* 7, 85.
Billingham, R. E., Krohn, P. L., Medawar, P. B. (1951) *Brit. med. J.* i, 1157.
Blocker, T. G. jun. (1951) Personal communication.
Brown, J. B. (1937) *Surgery*, 1, 558.
Cannon, B., Weisman, P., Quinby, W. C. (1952) *Ann. Surg.* (in the press).

References continued overleaf

MYSOLINE: A NEW DRUG IN THE TREATMENT OF EPILEPSY

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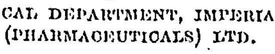
IN early 1949 Bogue and Carrington (1952) were working on the development and synthesis of compounds which modify or inhibit convulsions, and they found a new anticonvulsant drug now known as 'Mysoline.'* They showed that it protected laboratory animals against electrically or chemically induced convulsions. This drug, though closely related to phenobarbitone, is of a chemical type not hitherto used in man. Its chemical name is 5-phenyl-5-ethyl-hexahydropyrimidine-4 : 6-dione and its formula is :



It is a white crystalline substance, practically tasteless, chemically stable, and sparingly soluble in water (0·6 g. per litre at 37°C).

Mysoline has an extremely low toxicity, both acute and chronic, in all species of laboratory animals tested, including monkeys. It has no hypnotic action in doses many times that required to protect animals against electrically induced convulsions (Bogue and Carrington 1952).

In view of this favourable combination of properties a clinical trial in major epilepsy was made. An initial trial was carried out at the Crumpsall Hospital, Manchester, by Dr. G. E. Smythe, consultant neurologist. He confirmed its lack of toxicity—e.g., the absence of blood changes, and he found that a daily dose of the order of 0·8 g. would probably be necessary in mild cases.

The full clinical trial was carried out at the David Lewis Epileptic Colony. As the experimental work had suggested that mysoline would be of use against major epilepsy (grand mal), only patients with convulsions solely or predominantly of major type were included. They were chosen because of their eagerness to try a new form of treatment. They had all been in the colony for many years and had been treated for long periods with various anticonvulsants in full doses, both alone and in combination. Their condition at the start of the trial was the best we could achieve with existing drugs.

Accurate information about attacks in the previous few years was obtained from the chart recording the number of attacks per day which is kept for each patient in the colony. Major and minor attacks are entered separately. The nurse in charge of the house where the patient lives decides the nature of the attack: a minor attack is one in which unconsciousness lasts from a few seconds to a minute or two, and, though the patient may fall, there is no convulsion; a major attack includes unconsciousness, falling, and convulsion. The word "sensation" is used for what may be either the aura of an attack that does not develop or a very slight minor attack; these are not recorded.

The 40 patients who have been treated were originally divided into four groups, each of 5 men and 5 women. Groups 1 and 2 were made up of active, alert workers, whilst those in groups 3 and 4 had some complication, such as mental or physical deterioration. In a few cases mental deterioration was pronounced. The ages of the 40 patients were evenly distributed between 16 and 60.

Treatment of group 1 with mysoline began on Dec. 1, 1950, and of group 3 on Jan. 5, 1951. Groups 2 and 4 were controls for groups 1 and 3 respectively, and received inert tablets indistinguishable from those containing the active drug; we have found that when an epileptic patient starts any new treatment there is often a temporary improvement. The system of controls was dropped on Feb. 2 because, firstly, many patients in the control groups had noticed the different groups when the tablets were being given out and had realised that those in the opposite group were getting better while they were not; and, secondly, the difference in the response of the treated and control groups was so great as to make it virtually certain that the drug was

TABLE I—RESULTS IN GROUPS 1 AND 2

Case no.	Sex and age	Daily dose of mysoline (g.)	Incidence of fits per annum		% reduction	
			Nov. 1949–Oct. 1950	June–Nov. 1951	Major attacks	Major and minor attacks
1	F 28	1·2	M 25	2	92	92
			m 0	0		
2	F 50	1·0	M 51	0	100	100
			m 0	0		
3	F 42	1·6	M 224	30	86·6	75·7
			m 6	26		
4	F 47	1·4	M 81	0	100	100
			m 0	0		
5	F 39	1·4	M 34	0	100	100
			m 0	0		
6	M 25	1·6	M 71	58	18·3	18·3
			m 0	0		
7	M 40	1·2	M 68	0	100	100
			m 0	0		
8	M 43	1·4	M 29	30	(3·4)	(3·4)
			m 0	0		
9	M 24	0·8	M 24	0	100	100
			m 0	0		
10	M 31	1·6	M 36	0	100	54·7
			m 17	24		
11	F 35	1·2	M 91	12	86·8	86·8
			m 0	0		
12	F 29	1·6	M 31	31	0	0
			m 0	0		
13	F 52	1·4	M 36	0	100	100
			m 0	0		
14	F 26	1·6	M 52	4	92·3	93·2
			m 7	0		
15	F 46	1·4	M 47	0	100	100
			m 0	0		
16	M 25	1·0	M 43	0	100	100
			m 0	0		
17	M 33	1·0	M 22	0	100	100
			m 0	0		
18	M 35	1·4	M 34	0	100	100
			m 0	0		
19	M 26	2·0	M 47	4	91·5	91·5
			m 0	0		
20	M 29	2·0	M 21	0	100	(37·8)
			m 24	62		

M = major attack; m = minor attack; figures in parentheses represent % increase.

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* 'Mysoline' is the registered trade-mark of Imperial Chemical (Pharmaceuticals) Ltd. The drug is not yet freely available.

DR. BUTTERFIELD AND OTHERS: REFERENCES—*continued*

Colebrook, L. (1950) A New Approach to the Treatment of Burns and Scalds. London.
Corcoran, A. C., Page, I. H. (1948) *J. Lab. clin. Med.* 33, 1326.
Ellison, E. H., Zollinger, R. M., Martin, B. C., Williams, R. D., Clatworthy, H. W., Hamwi, G. (1952) *Ann. Surg.* (in the press).
Finland, M., Kass, E. H., Ingbar, S. H. (1950) *Proceedings of the First Clinical* A.C.T.H. Conference. Philadelphia; p. 529.
Fisher, R. A., Yates, F. (1949) Statistical Tables for *Biological, Agricultural, and Medical Research.* Edinburgh.
Himsworth, H. P., Kerr, R. B. (1939) *Clin. Sci.* 4, 1.
Kearns, J. E. jun., Reid, S. E. (1949) *Plastic Reconstruc. Surg.* 4, 502.
Longmire, W. P. jun. (1951) Personal communication.
— Stone, H. B., Daniel, A. S., Goon, C. D. (1947) *Plastic Reconstruc. Surg.* 2, 419.
Medawar, P. B. (1944) *J. Anat., Lond.* 78, 176.
— (1946a) *Brit. J. exp. Path.* 27, 9.
— (1946b) *Ibid*, p. 24.
Mote, J. R. (1950) Personal communication.
Mulholland, J. H. (1951) *Ibid.*
Randolph, T. G. (1944) *J. Allergy*, 15, 89.
Saunders, C. B., Moore, R. H. (1950) *Amer. J. Surg.* 80, 637.
Soffer, L. J., Shwartzman, G., Schneirson, S. S., Gabrilove, J. L. (1950) *Science*, 111, 303.
Sparrow, E. M. Cited by Billingham et al. (1951).
Thorn, G. W., Forsham, P. H., Prunty, F. T. G., Hills, A. G. (1948) *J. Amer. med. Ass.* 137, 1005.
Tompsett, S. L. (1949) *J. clin. Path.* 2, 126.
Trueta, J. (1943) War Surgery. St. Louis.
Whitelaw, M. J. (1951) *J. Amer. med. Ass.* 145, 85.

TABLE II—RESULTS IN GROUPS 3 AND 4

Case no.	Sex and age	Daily dose of mysoline (g.)	Incidence of fits per annum		% reduction	
			Nov. 1949–Oct. 1950	June–Nov. 1951	Major attacks	Major and minor attacks
21	F 50	1·6	M 1602 m 79	1406 12	12·2	15·7
22	F 16	1·6	M 110 m 171	79 5	28·2	70·1
23	F 40	1·6	M 38 m 0	60 0	(57·9)	(57·9)
24	F 43	1·6	M 74 m 0	22 0	70·3	70·3
25	F 26	1·6	M 66 m 96	58 38	12·1	40·8
26	M 24	1·6	M 61 m 0	30 0	50·8	50·8
27	M 43	1·6	M 63 m 0	30 0	52·4	52·4
28	M 51	1·6	M 81 m 0	34 0	58·0	58·0
29	M 46	1·6	M 73 m 78	0 12	100	92·1
30	M 29	1·6	M 83 m 0	42 0	49·4	49·4
31	F 49	1·4	M 74 m 79	3 8	96	92·8
32	F 21	1·2	M 272 m 133	2 0	99·3	99·5
33	F 60	1·0	M 60 m 25	6 1	90·0	91·8
34	F 29	1·2	M 62 m 26	0 0	100	100
35	F 38	1·2	M 73 m 0	0 0	100	100
36	M 40	1·6	M 47 m 0	4 32	91·5	23·4
37	M 41	1·6	M 77 m 38	46 22	40·3	40·9
38	M 28	1·4	M 86 m 0	80 0	7·0	7·0
39	M 30	1·6	M 106 m 0	66 0	37·7	37·7
40	M 31	1·6	M 95 m 17	44 38	53·7	26·8

M = major attack; m = minor attack; figures in parentheses epresent % increase.

esponsible. Thereafter mysoline was given to all four groups.

Tablets containing 0·2 g. of mysoline were used: at first a dose of 0·2 g. twice daily was added to whatever reatment was being given; and the dose was then gradually increased to 0·8 g. daily, when the original reatment was stopped. Further increases, in steps of 0·2 or 0·4 g., were dictated by persistence of attacks and he tolerance of the patient to the drug. The only exceptions to this rule were that groups 2 and 4 started on 0·2 g. *three* times a day and in some cases the dose was raised to 1·0 g. daily without waiting to see if 0·8 g. would be sufficient. In groups 1 and 3 complete withdrawal of previous treatment lasted six to eight weeks, and in groups 2 and 4, when the value and safety of mysoline was clear, this time was reduced to two weeks. Except for a short period at the start in groups 2 and 4, the drug was given twice daily (morning and evening). If the daily dose contained an odd number of tablets, the odd tablet was given in the evening.

RESULTS

Our investigation suggested that the optimum daily dosage of mysoline rarely exceeds 1·6 g.; increased control by larger doses was sometimes offset by undesirable symptoms.

Incidence of attacks

Tables I and II give the results in individual patients from June to November, 1951, when all but 2 were taking 1·6 g. or less per day. Improvement was assessed by doubling the number of attacks during this period and expressing the result as a percentage of the number which occurred from November, 1949, to October, 1950.

In estimating the complete response to treatment (table III) the patients were divided into four classes: free from attacks; much improved (where the reduction of attacks was two-thirds or more); some benefit (one-third to two-thirds reduction); and no improvement (less than a third).

The results show that mysoline is an effective drug for controlling major epilepsy. Of our 40 patients 32 (80%) were improved and 12 (30%) were completely free from attacks of all kinds. Only 1 patient was significantly worse. Better results were obtained in groups 1 and 2 than in groups 3 and 4, but there were some notable exceptions (cases 29 and 32). Generally speaking those with marked mental deterioration did not respond so well. In 2 patients whose major attacks were completely eliminated, the minor attacks definitely increased.

But these figures do not give a complete picture of the improvement in many patients. Convulsions which still occurred were often much less severe and complete than before, and recovery was much quicker. The patients themselves said that they were able to resume work more quickly and that the "hangover" time was less. Patients whose attacks came on only at night were thus able to do a full day's work. Other benefits noted with doses up to 1·6 g. daily were the absence of hypnotic effect; a feeling of fitness; an improved ability to perform small tasks; mental alertness instead of the former dullness; and a new interest in pastimes, such as dancing.

Side-effects

With doses below 1·6 g. daily there were only a few very mild and transient side-effects. One woman developed a morbilliform rash on the arms and legs after a week's treatment, but this only lasted a few days. One man complained of slight nausea and abdominal discomfort on the third day of treatment. He has since taken 2·0 g. daily for nine months without ill effect. In neither case was mysoline stopped or reduced. 2 other patients had transient and mild feelings of drunkenness on the first two days of treatment. In a more recent series this effect has been more definite. At the start of treatment several patients have complained of dizziness, disturbance of accommodation, listlessness, and difficulty in rousing from sleep. One man had a slight nystagmus on extreme lateral vision. All these symptoms passed off in a few days and treatment was not interrupted.

TABLE III—ANALYSIS OF 40 PATIENTS TREATED WITH MYSOLINE

—	Free from attacks	Much improved	Some benefit	Not improved
Major attacks	37·5 %	25 %	17·5 %	20 %
Major and minor attacks	30 %	27·5 %	20 %	22·5 %

Regular urine examinations and blood-counts (red-cell and total and differential white-cell counts) were made on every patient and showed no abnormality at any time.

In 13 patients the upper limit of dosage reached 2·0 g. per day and in 4 1·8 g. per day. After receiving 2·0 g. a day for three weeks, 4 of the 13 became lethargic, slow in speech, and somewhat ataxic, and they complained of difficulty in getting out of bed in the morning. When the drug was withdrawn in 1 case and reduced to 1·2 g. in the other 3 the symptoms promptly disappeared. We are satisfied that 2·0 g. is a high daily dose and, with 2 exceptions (cases 19 and 20), all the patients were reduced to 1·6 g. or less a day. The exceptions were big, strongly built men who were obviously benefiting from 2·0 g. daily, and have remained on it for nine months.

One woman (case 12) died from asphyxia in a major convulsion. She had not benefited from mysoline and did not take her tablets regularly. At necropsy microscopic examination of the kidneys, liver, lungs, brain, suprarenals, thyroid, and ovaries showed no abnormality other than asphyxial changes.

CONCLUSIONS

Mysoline greatly reduces the number and severity of attacks in major epilepsy. An effective dose up to 1·6 g. daily gives few side-effects and does not seem to make the patients sleepy. Hypertrophy of the gums and abnormal blood changes did not occur in this series. The absence of toxic effects means that mysoline can be safely used in all types of practice without laboratory control. No conclusions can be drawn about its action in petit-mal or other types of epilepsy.

It would be an advantage to use tablets of 0·25 g. in future to reduce the number of tablets and yet preserve the flexibility of dosage.

The change from old to new treatment was uneventful and, until further experience is gained the previous drug should be withdrawn gradually over two weeks. 0·25 g. of mysoline twice daily should be added for three days and then increased by 0·25 g. every three days up to a daily total of 1 g. Further increases up to a daily total of 1·6 g. may be made if necessary. Withdrawal of previous treatment should begin on the fourth day and should be complete by the end of the second week. A few patients may be controlled by as little as 0·75 g. per day, and *certain cases may benefit from as much as 2 g. daily.*

SUMMARY

A new anticonvulsant, 'Mysoline,' was given to 40 patients who were continuing to have major epilepsy despite other forms of treatment.

Doses up to 1·6 g. daily produced no serious side-effects or sleepiness. Attacks were reduced in 80% of patients and completely stopped in 30%.

We are indebted to Dr. O. L. Davies for a statistical analysis *of the early results, and for advice on the compilation of* tables I and II.

REFERENCE

Bogue, J. Y., Carrington, H. C. (1952) To be published.

HYPOPLASIA AND APLASIA OF THE VAGINA TREATED WITH ŒSTROGENIC HORMONE IMPLANTS

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THOUGH congenital vaginal aplasia is not extremely rare, estimates of its incidence vary within broad limits: Bryan et al. (1949) cite Owen's assessment of 1 in 250,000 female hospital admissions; give the incidence in their own practice as 1 in 4000 female patients; and cite Engstadt as *finding 1 in 5000 female births.*

I wish to draw attention to the value of œstrogenic hormone implants in treating this condition. A case of severe vaginal hypoplasia and a case of congenital vaginal aplasia responded very satisfactorily to such treatment.

CASE-RECORDS

Case 1.—A married woman, aged 21, attended the gynæcological outpatient department at Guy's Hospital in January, 1948, complaining that during the one and a half years of her married life attempts at sexual intercourse had always been extremely painful, and penetration had never been effected, for which reason her husband was seeking an annulment of the marriage. She had never menstruated. At the age of 3 years she had been sent to a home for six months with gonococcal vulvovaginitis. *At the age of 7 years she underwent* an operation for bilateral ovarian cysts. Reference to her previous notes revealed that the right ovary, being completely replaced by a cyst 8 cm. in diameter, had been removed in its entirety. It had been possible to conserve a small portion of her left ovary which bore a cyst 5 cm. in diameter. The microscopist's report on one of the cysts stated it to be "a serous cystoma with few papillary processes and little or no proliferation."

On examination the patient was an essentially feminine an attractive girl. Mammary development was almost non existent, her pubic hair was very scanty, and her vulv infantile. Her vagina was represented by a small passag 1·5 cm. long and 0·5 cm. in diameter. On rectal examinatio a small cervix and very small corpus uteri were thought to b palpable.

Treatment and Progress.—On Jan. 23, 1948, eight pellets each of 25 mg. of œstradiol, were implanted in the subcutaneou tissue of her thigh. By May 14, 1948, her breasts had grow appreciably and her vagina was 6 cm. long although still ver narrow. On Nov. 21, 1948, she was re-examined. Th development of her breasts had continued, but they were stil subnormal. Her pubic hair had a normal female appearanc *and her vulva was normal. Her vagina* had increased i diameter and now readily admitted an index finger, but onl for a distance of 6 cm. She stated that sexual intercourse wa possible but not entirely satisfactory because of the shortnes of the vagina. Her marriage, however, was now happy. Sh had not menstruated. Under anæsthesia the cervix wa found and dilated. A sound was passed for 5 cm. into th uterus. A curettage specimen showed "squamous epitheliu only." On Dec. 21, 1948, three pellets of stilbœstrol, each o 100 mg., were implanted subcutaneously in her thigh. B Jan. 14, 1949, sexual intercourse was described as satisfactor and still improving. The vagina would admit two fingers fo 7 cm.

Follow-up.—On Oct. 23, 1951, nearly three years after th last implant, this patient was seen for a final follow-up. Sh still had not menstruated. Her breasts had regressed a little (she had lost a stone in weight while nursing her husban recently), but were within the limits of normality, as wer her growth of axillary and pubic hair. On inspection th vagina revealed little change in length, but being less rigi in diameter permitted two fingers which were comfortabl accommodated to depress the vault to a distance of 9 cm from the introitus. Sexual intercourse was taking plac about once a week, and she occasionally obtained an interna orgasm. Her husband regarded their relationship as normal

Case 2.—A married woman, aged 24, attended the gynæcological outpatient department at Guy's Hospital in May, 1948, because she had not "developed normally." She had first noticed her deficiency when at puberty her breasts had *not grown and she had not begun to menstruate.* In the Army, where for four years she had served as a female dispatch-rider, a specialist had told her that she had no uterus. In November, 1947, there had been removed from her right groin a tender tumour which had been present for a year. The surgeon reported on this tumour that "it was such an obvious testicle, with epididymis and vas deferens" that he had not sent it for section. Since then she had noticed a similar lump from time to time in the left groin. She stated that she felt essentially female, had a Canadian fiancé, and wanted advice about marriage.

On examination her head and face were those of a normal, not unattractive, female. Her chest was that of a young man, with no more breast development, but without hair. Her axillary and pubic distribution of hair, however, was *that of a young woman.* Her abdomen was normal, bearing an operation scar in the right inguinal region. No tumour was (or ever has been) seen in the left groin. The perineum comprised a normal anus and two small rounded labia which led in front to a large clitoris, 2 cm. long and 1 cm. broad, with a well-developed prepuce. The external urethral orifice was situated behind the base of the clitoris, but no vagina could be seen.

A month later, examination under *anæsthesia confirmed* these findings, except that a small vaginal passage was found which would just admit a small probe for 0·5 cm. No uterus could be palpated.

Treatment and Progress.—On June 26, 1948, a subcutaneous implant of three pellets of œstradiol 100 mg. each was made in her thigh. By Dec. 8, 1948, her breasts had grown appreciably; her clitoris was possibly a little larger; her vagina readily admitted an index finger for 7 cm.; the vault of the vagina was smooth; and there was no evidence of cervix or corpus uteri. She had married recently, and her husband had left immediately for Canada, where she hoped to join him when her treatment was completed. Sexual intercourse had not been attempted. Two days later six pellets of œstradiol, each of 50 mg., were implanted subcutaneously in her thigh. *Since her vagina would now take a* glass dilator, she was provided with sizes 2 and 3 and instructed to use them at night, lubricated with 'Menformon' ointment. Two months later (February, 1949) the vagina admitted two fingers for 7 cm. A no. 4 dilator was provided.

Follow-up.—On Sept. 10, 1950, she wrote: "Things are just about the same as when you last examined me. I didn't have any further breast development and as the hormones are almost exhausted they are receding gradually now. The only other development is the vagina, but in width only and not in length. We found this last difficult at first but have adjusted ourselves accordingly. I had a great deal of pain during intercourse for a month after I got here, and also a great deal of bladder trouble, sometimes visiting the toilet 3 to 4 times in an hour. This lasted 6 or 8 weeks and was accompanied by pain in the clitoris which has remained static and shows no sign of getting any smaller. My husband is well developed, but he says not excessively so, and we are able to accomplish sexual relations with ease, which shows my progress."

DISCUSSION

Case 1 was virtually a female castrate and there was good evidence of ovarian deficiency. Case 2 was almost certainly a male pseudohermaphrodite and presumably had no ovarian tissue at all. It was reasonable therefore to expect that the former would, and to postulate that the latter might, respond to treatment with œstrogens. The questions arise how often evidence of œstrogen deficiency (possibly as an ætiological factor) is present in congenital vaginal aplasia, and whether there is not a good case for using œstrogen therapy in preference to other methods when this state of affairs is either manifest or suspected.

Incidence of Œstrogen Deficiency

Frank (1938), discussing congenital vaginal aplasia, states that "these individuals *with few exceptions*, are fully feminine." McIndoe (1950) likewise states that ovarian tissue is *most commonly* present, but records no estimate of its adequacy as indicated, for example, by the state of breast development. Bryan et al. (1949), reporting on 100 patients with this condition, are more explicit: 2 had infantile genitalia and no pubic hair, and in 61 "because of the secondary sexual characteristics it seemed that *some ovarian tissue* was undoubtedly present." It is not stated, however, whether it appeared to be adequate. 26 of the 100 patients were subjected to laparotomy, and 1 was found to have no ovaries. In 9 herniorrhaphies 7 sacs contained an ovary, 1 sac contained a testis, and 1 an ovotestis. Miller et al. (1945), reporting 16 cases, describe the ovaries as being present in all, but mention specifically "patients with underdeveloped secondary sex characteristics." Wharton (1946) mentions having successfully treated young women who had no ovaries at all and male pseudohermaphrodites, and concludes that the chance of making and preserving a functioning vagina is distinctly less if ovarian function is absent.

From these facts and implications one is provided with good reason to believe that an appreciable number of patients with congenital vaginal aplasia are deficient in ovarian activity.

Œstrogen Therapy

Operations after the fashion of Baldwin, utilising loops of ileum or of sigmoid colon, and of Schubert, using rectum, have now become almost obsolete. All the operations which have followed and displaced them entail the construction of a cavity between the bladder and the rectum. They differ in the manner in which this cavity is lined. The use of pedicle grafts from the thigh and labia minora has for the most part been given up, and in general the present practice is either to rely on the power of the cavity to epithelise itself, or to use a single-piece Thiersch graft. With these two operations excellent results are being obtained at many clinics with a low morbidity-rate and a very low mortality-rate; but most surgeons will not find, as Counseller (1948) does, that "the risk of operation is practically non-existent." Counseller emphasises how extremely commonly gross anomalies of the renal tract are associated with congenital vaginal aplasia (6 pelvic kidneys, 5 solitary kidneys, and 8 other abnormalities in 35 patients), which must add to the hazards that will of necessity accompany a pelvic operation of this magnitude in any but the most skilled hands (Counseller 1948, Bryan et al. 1949).

There is undeniable virtue in any treatment that entails neither operation nor admission to hospital, provided it is practicable and the results are satisfactory. One such method, described by Frank (1938, 1940), has apparently been followed by excellent results. Using his technique the patient presses a tubular instrument —e.g., a hard glass test-tube—for half an hour twice a day, against the skin of the vestibule behind the external urethral meatus. When a small vagina has been produced, dilators are used to enlarge the cavity in depth and diameter to the required dimensions. Perhaps the most cogent criticism of this method is that it demands of the women a patience and persistence that must, at least occasionally, border on the obsessional, and which, being focused on the genitalia, may be undesirable. On the other hand, once an adequate vagina has been produced, there is not the need for regular sexual intercourse or dilatation to prevent shrinkage that there is after the surgical procedures.

The suggestion that œstrogens might be used with benefit to these patients is not new. Campbell (1941), describing a case treated by Frank's method, recorded that the patient felt she had been considerably helped by the prescription of œstrin pessaries to make the mucosa more pliable, and Brady (1945), in similar circumstances, used œstradiol ointment. Miller et al. (1945) thought that œstrogen therapy might be helpful in the postoperative period as a means of stimulating epithelial growth. Wharton (1946) reported that, after Thiersch-grafting a surgically produced cavity, he used œstrogens in large doses to help maintain the vaginal calibre and the epithelium, but the results were indifferent. Further, Counseller (1948), considering those patients in whom a space had been fashioned but no graft used, gave some of the credit for epithelisation to the remnants of the Müllerian ducts, which, as buds of squamous epithelium, can be found during the dissection beneath the bladder, and suggested that this epithelisation might be accelerated by the administration of œstrogenic substances.

It seems, however, that no consideration has been given to the possibility of treating these patients with œstrogenic hormone alone. In the light of the favourable results achieved in the two cases reported here such therapy seems worthy of trial in selected cases of congenital vaginal aplasia; for, as has been shown, there is evidence that an appreciable number of these patients are deficient in ovarian function. Nor is it beyond the bounds of analogy to postulate that in some cases with normal secondary sexual characteristics there is a local vaginal lack of response to ovarian hormones which might be overcome by excessive œstrogenic stimulation. The virtue of a treatment which entails the least surgery, no admission to hospital, and no assiduous application of instruments to the genitalia is obvious.

CONCLUSION

In planning remedial treatment for young women with congenital vaginal aplasia one should be influenced not only by "the anatomical findings, the temperament, the marital status, the intelligence and the coöperation of the woman one is treating" (Brady 1945) but also to some extent by the degree and nature of gonad function.

SUMMARY

The cases of a female castrate with considerable vaginal hypoplasia and of a male pseudohermaphrodite with congenital vaginal aplasia are reported. In both the vaginal dimensions improved satisfactorily in response to implantations of œstrogenic hormone.

Ovarian deficiency is present in an appreciable proportion of cases of congenital vaginal aplasia.

The treatment of congenital vaginal aplasia is briefly reviewed to demonstrate by comparison the advantage of œstrogen implantation therapy, which entails no major surgery, no admission to hospital, and no assiduous attention to the patient's genitalia.

It is a pleasure to express my indebtedness to Mr. A. J. McNair and Mr. F. Cook for their help and permission to treat their cases, and to Dr. P. M. F. Bishop for his advice about the implants.

REFERENCES

Brady, L. (1945) *Ann. Surg.* **121**, 518.
Bryan, A. L., Nigro, J. A., Counseller, V. S. (1949) *Surg. Gynec. Obstet.* **88**, 79.
Campbell, K. (1941) *Med. J. Aust.* ii, 650.
Counseller, V. S. (1948) *J. Amer. med. Ass.* **136**, 861.
Frank, R. T. (1938) *Amer. J. Obstet. Gynec.* **35**, 1053.
— (1940) *N.Y. St. J. Med.* **40**, 1669.
McIndoe, A. (1950) *Brit. J. plastic Surg.* **2**, 254.
Miller, N. F., Willson, J. R., Collins, J. (1945) *Amer. J. Obstet. Gynec.* **50**, 735.
Wharton, L. R. (1946) *Ibid*, **51**, 866.

PULSUS PARADOXUS

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Gauchat and Katz (1924) defined pulsus paradoxus as "a rhythmic pulse occurring in natural breathing which shows a waxing and waning in size during respiration, evident on palpation in all accessible arteries," and they recognised that it occurred in two groups of cases—those with enhanced intrathoracic pressure variation, and those with cardiac tamponade. They had no way of recording the blood-pressure in their patients and had to rely on sphygmograms.

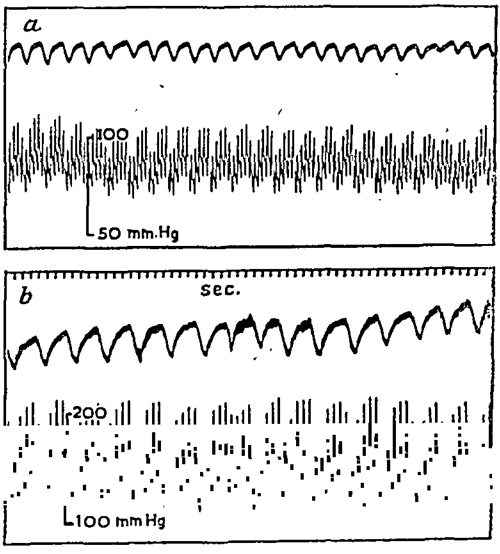

Fig. 1—Spirogram and blood-pressure from two patients in asthmatic attacks. Both exhibited pulsus paradoxus. In this and in all the other records inspiration is shown by a downward movement of the spirogram.

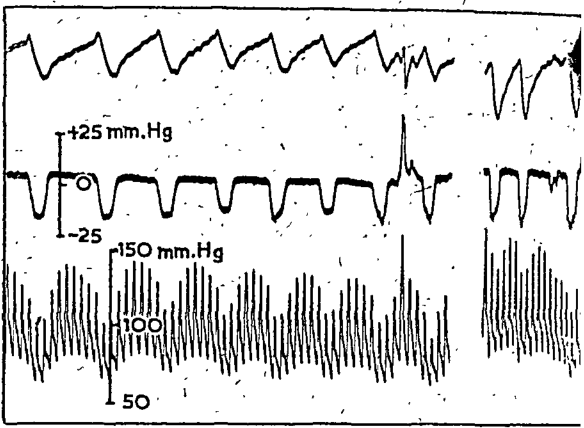

Fig. 2—Spirogram, intrathoracic (œsophageal) pressure, and bloo pressure from a patient with asthma and pulsus paradoxus. Shar spike in pressure records corresponds to a single cough.

In this article we present examples of blood-pressur records from both types of case, and discuss the natur and origin of the abnormalities observed. We shall us the term "pulsus paradoxus" in the clinical sense a defined above. Pressures were measured with a capacitance manometer (Hansen 1949), and chest expansio was recorded with a Manning spirograph.

ENHANCED INTRATHORACIC PRESSURE VARIATION

Fig. 1 shows spirogram and blood-pressure record from two patients, both of whom were having asthmati attacks and exhibiting pulsus paradoxus. In one ther is a considerable phasic variation in pulse pressure, bu in the other this is inconspicuous. The feature commo to both tracings is the abrupt downward movement o both systolic and diastolic pressures at the start o inspiration.

Fig. 2 is the record of chest movement, intrathoraci (œsophageal) pressure, and blood-pressure in a thir asthmatic patient. A similar type of sudden downwar dislocation of the blood-pressure trace is present, an this is seen to coincide with a sharp drop in intrathoraci pressure. The second part of the record shows that, when inspiration is delayed, the pulse pressure decrease smoothly during the prolonged expiration, but that n sudden drop of diastolic pressure occurs until the nex inspiration. By comparing corresponding beats, counted from the preceding inspiration, in cycles of varying length one may ascertain that inspiration has little or no instantaneous effect on pulse pressure, but depresses equally the systolic and diastolic pressures that would otherwise obtain. The magnitude of this depression is about half the inspiratory drop in intrathoracic pressure. By contrast, almost the whole of the positive intrathoracic pressure wave associated with a cough is reproduced in the blood-pressure.

Interpretation

One may summarise and interpret these findings as follows. Increased airway resistance leads to an augmentation and distortion of the intrathoracic pressure variation. The augmentation in severe asthma may be fivefold —say from 5 to 25 mm. Hg. The distortion consists in a change from the normal, approximately triangular, wave form to an approximately rectangular one (fig. 3). Thus not only is the total pressure change greatly increased, but so also is the rate of change of pressure. The increased pressure swing will tend to increase the normal-phasic variations of pulse pressure, but that this is not necessary for the occurrence of pulsus paradoxus is shown by fig. 1*b*. The fundamental mechanism of this type of pulsus paradoxus is the direct transmission through the aortic wall of the almost square-wave impact of the abnormal intrathoracic pressure changes. Such rapid pressure changes are well reproduced in the arterial system, whereas slower changes are not. Only a part of the applied pressure appears in the arteries, since the pressure is applied to the intrathoracic vessels alone and the hydraulic capacitance of the remaining arteries shunts the effect. During a cough the abdominal as well as the thoracic pressure rises and a much greater proportion of the total arterial system is subjected to pressure.

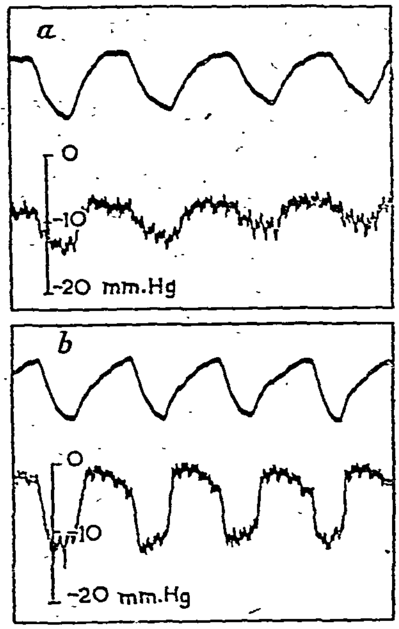

Fig. 3—Spirogram and intrathoracic pressure in a normal person: upper part shows unobstructed breathing; in the lower part the subject is breathing through resistances arranged to simulate the effects of a mild attack of asthma.

CARDIAC TAMPONADE

Fig. 4*a* is a record from a case of pericardial effusion with severe cardiac tamponade and pulsus paradoxus. Fig. 4*b* is from the same case after aspiration of the pericardium. The jugular pressure was still somewhat raised, but there was no pulsus paradoxus. Fig. 4*c* is from a milder case of pericardial effusion. The jugular pressure was just raised: there was no pulsus paradoxus. Fig. 4*d* is from a normal person and is included for comparison. The right-hand section of each tracing shows the effect of an expiratory pause on the blood-pressure—by this manœuvre the effects of an inspiration can be separated from the delayed effects of the preceding expiration. It will be seen that, in the tracings from patients with pericardial effusion, and in contrast with the normal, inspiration causes a distinct and immediate lowering of pulse pressure. As would be expected, the effect is most striking in the record associated with pulsus paradoxus. Further investigation of this patient showed that there was no exaggeration of the respiratory changes in intrathoracic pressure, and that inspiration was associated with an increase of right ventricular systolic and pulse pressures, suggesting an inspiratory increase of right ventricular filling and ejection, such as occurs in a normal person.

Interpretation

We interpret our findings as indicating that, when a pericardial effusion is present, inspiration causes an immediate decrease in left ventricular stroke volume. If we assume that this is due to an inspiratory decrease in left ventricular effective filling pressure, we have still to explain how the effusion brings this about.

Katz and Gauchat (1924) injected oil into the pericardium of dogs and thus produced exaggerated respiratory blood-pressure variations. They observed that, when the quantity injected was small, the intrapericardial pressure closely followed the intrathoracic pressure; but that, as they increased the amount injected, the intrapericardial pressure varied less than the intrathoracic. This change, which implies an inspiratory decrease in the effective filling pressure of the left ventricle, they explained as follows:

> "This is undoubtedly due to the relative inelasticity of the pericardium and the fact that it rapidly reaches the limit of its elasticity as more and more fluid is forced into it. Under such conditions comparatively slight pressure variations . . . are unable to stretch or compress the rigid pericardium further."

It should be noted that they considered that the filling of the right ventricle was also decreased during inspiration.

This explanation has been generally accepted without comment (Wiggers 1949), but we believe it to be physically inexact. We suggest that the following is a truer statement of the case. Normally the inspiratory drop in intrathoracic pressure is equally applied to the left ventricle and pulmonary veins. No change in left ventricular effective filling pressure ensues and no material immediate change in filling or ejection. Right ventricular effective filling pressure does increase, because the systemic veins are largely extrathoracic. This increased filling of the right ventricle is without effect on the left. When the pericardium is distended, the effect is different. In that case increased filling of one ventricle will increase the intrapericardial pressure and hence tend to hinder filling of the other. With inspiration the intrapericardial pressure starts to fall, but does not fall as far as does the intrathoracic pressure, because of increased right ventricular filling. Decreased filling of the left ventricle thus occurs.

The physical considerations outlined above have been checked by constructing a simple model (fig. 5). When the "pericardium" P is slack, lowering the pressure in the box causes increased filling of R but no change in L.

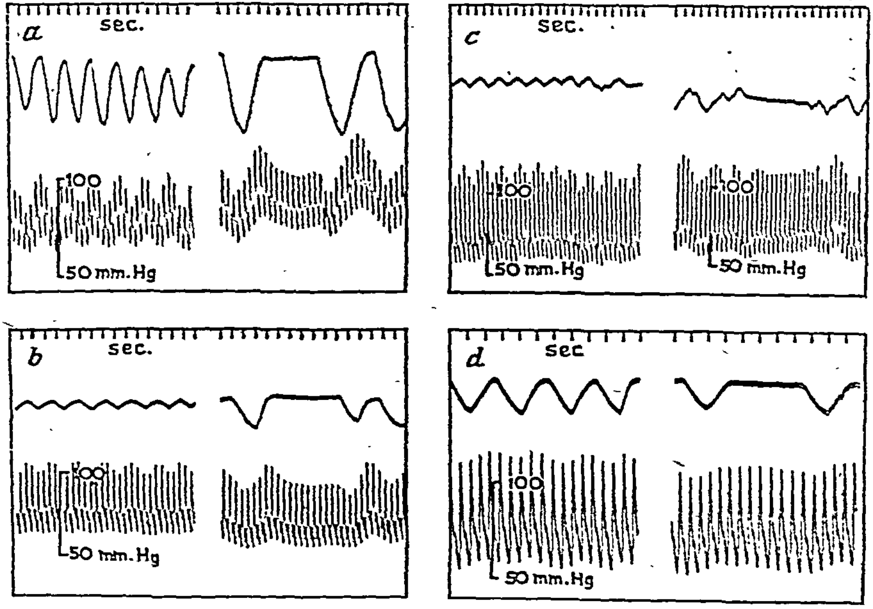

Fig. 4—Spirogram and blood-pressure in: *a*, a case of pericardial effusion and cardiac tamponade; *b*, same case after pericardial aspiration; *c*, a patient with a lax pericardial effusion; *d*, a normal person. The sensitivity of the spirogram is not the same in the different records.

When sufficient fluid is injected into the "pericardium" to render it taut, lowering the box pressure causes an emptying of L. This effect is abolished if the entry to R is clamped at X.

It was stated above that inspiration was normally without material effect on left ventricular ejection. In fact some normal people show no effect at all, whereas others have a decrease in pulse pressure of a few mm. Hg for one beat. T[illegible]ng of the ventricles is not always [illegible] which is scarcely surprising when it is remembered that the superficial layer of ventricular muscle embraces both ventricles.

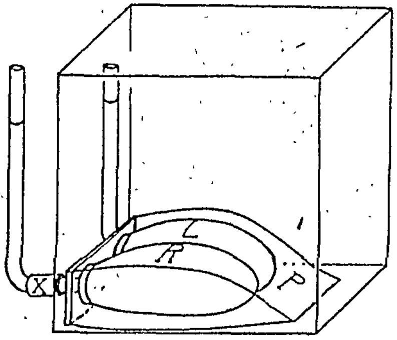

Fig. 5—Sketch of model referred to in text. "Ventricles" are of thin rubber, and "pericardium" of soft but relatively inelastic plastic sheet.

DISCUSSION

We have accepted the clinical definition of pulsus paradoxus given by Gauchat and Katz (1924). For the sign to be present, it is probable that at some point in inspiration a pulse must have its systolic peak 10–15 mm. Hg below its predecessor. If the beat-to-beat variation is small, very large over-all pressure swings may exist without being apparent to the finger. On the other hand, with the sphygmomanometer the over-all swing alone can be recognised. It follows that, if a more objective definition in terms of sphygmomanometer readings is attempted, the nature and significance of the sign will be changed. In certain circumstances normal people may have over-all pressure swings greater than any of those illustrated here: we believe, however, that pulsus paradoxus in the clinical sense is always pathological.

Pulsus paradoxus in respiratory obstruction is not of great clinical interest. It may be readily produced in a normal person by breathing through a suitable resistance; hence its occurrence does not signify any circulatory fault. In cardiac tamponade the sign may occasionally be of diagnostic value. However, it is not very common and, when it occurs, there are usually other grounds for suspecting pericardial effusion. It is natural to seek to recognise the characteristic disturbance in a less fully developed form and thus to extend its usefulness. Our experience suggests that the manœuvre illustrated in fig. 4 may prove of value in some cases. We would emphasise that inspection of the blood-pressure record during normal breathing is inadequate: it is essential to separate, by a suitable respiratory pause, the effects of inspiration and expiration.

SUMMARY

Records of the blood-pressure in patients exhibiting pulsus paradoxus are presented.

The mode of production of the sign is discussed.

A manœuvre for demonstrating the pulse abnormality in pericardial effusion when clinical pulsus paradoxus is absent is described.

REFERENCES

Gauchat, H. W., Katz, L. N. (1924) *Arch. intern. Med.* 33, 350.

Hansen, A. T. (1949) Pressure Measurement in the Human Organism. Copenhagen.

Katz, L. N., Gauchat, H. W. (1924) *Arch. intern. Med.* 33, 371.

Wiggers, C. J. (1949) Physiology in Health and Disease, 5th ed., London; p. 728.

BONE-MARROW CULTURES OF KOCH'S BACILLUS*

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BONE-MARROW cultures of Koch's bacillus have been made in the past, but only very few. Koizumi (1925), using potato medium, cultured bone-marrow from 30 patients who died of tuberculosis, and obtained 70% positive results. Leitner (1949) cultured sternal bone-marrow from 54 patients with disseminated tuberculosis and obtained only 1 positive result. Stahel (cited by Schleicher 1950) found tubercles in bone-marrow sections in miliary tuberculosis (1 case). Schleicher (1946) also found tubercles in the bone-marrow of miliary tuberculosis (8 cases).

The present paper deals with bone-marrow cultures from 65 children, aged fourteen or less, with tuberculosis, mostly primary complexes.

METHOD AND MATERIAL

Bone-marrow was aspirated either from the sternum or from the iliac crest in amounts of 0·1–0·2 c.cm. The material was inoculated directly into Löwenstein and Petragnani media. Smears were also made from the same material to make sure that it was really bone-marrow. Of 65 cases examined 16 gave positive cultures. In 12 of these the organism was of the human type and in 4 it was of bovine type. All the positive cultures were injected into guineapigs: these died, and the presence of disseminated tuberculosis was verified by necropsy.

BONE-MARROW CULTURES

Form of tuberculosis		Age of patient (yr.)											
		0–2			2–6			6–14			Total		
		Positive	Negative	Total	Positive	Negative	Total	Positive	Negative	Total	Positive	Negative	Total
Primary complex	Adenitis	3	7	10	7	20	27	2	5	7	12	32	55
	Pleurisy	—	—	—	—	6	6	—	2	2	—	8	
	Atelectasis	—	—	—	—	2	2	—	1	1	—	3	
Tuberculous pneumonia and bronchopneumonia		—	—	—	2	—	2	—	—	—	2	—	2
Disseminated and miliary		1	2	3	1	4	5	—	—	—	2	6	8
Total ..											16	49	65

The accompanying table shows that many positive cultures were obtained from cases with a primary complex and little general involvement. It is difficult to say what the importance of this finding is from the point of view of pathogenesis and prognosis of tuberculosis.

Research is now going on here to elucidate other questions arising from these findings—e.g., how long the tubercle bacillus remains in the bone-marrow during e evolution of the primary complex; and how the sults of bone-marrow cultures compare with those of ood-cultures and gastric-juice cultures.

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* Abridged from a paper read before the Greek Pædiatric Society on May 31, 1951.

We should like to thank Prof. K. Melanides for inoculating l observing the guineapigs at the laboratory of the High riculture School.

ADDENDUM

While we were still conducting this investigation orowitz and Gorelick (1951) reported that they had ated 3–5 c.cm. of bone-marrow and inoculated it [illegible] to a special medium, and had prepared direct smears ith the same material. In 20 cases of tuberculosis they otained 5 positive cultures and 14 positive smears.

REFERENCES

orowitz, J., Gorelick, D. F. (1951) *Amer. Rev. Tuberc.* 63, 346.
oizumi, T. (1925) *Z. Tuberk.* 42, 208.
eitner, S. J. (1949) Bone-marrow Biopsy. New York; p. 406.
hleicher, E. M. (1946) *Amer. Rev. Tuberc.* 53, 115.
— (1950) Meeting of Mississipi Valley Trudeau Society, Sept, 22.

STERNAL OSTEOMYELITIS

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PRIMARY osteomyelitis of the sternum is rare. Vaughan 918) described 1 case and mentioned that Drews (1910) ould find only 13 in the literature. The clinical picture n the following case was remarkable.

An Army cook, aged 26, was admitted to hospital in Italy n Aug. 15, 1945, with three weeks' history of pain and ghtness in the chest which had become more severe in the receding forty-eight hours. Apart from a temperature of 9°F no abnormal physical signs were found. Nine months reviously he had bruised an area over his manubrium sterni gainst a kitchen table. The bruise faded in a few days. He ad not been subject to any skin eruptions.

Examination.—Dr. Raymond Moir asked me to see the atient on Aug. 22 because a hot, painful, and acutely tender welling had developed over the manubrium sterni, with eddening of the overlying skin. The pectoral muscles were cutely tender; and to obtain any relief from pain the patient was obliged to sit with his feet over the end of the bed and with his elbows close together on a bed-table in front of him. His temperature was 104°F, his pulse-rate was 120, and he was desperately ill.

Investigations.—Radiographs of the chest, sternum, and dorsal spine appeared normal. White-cell counts on Aug. 18 and 21 were 8600 and 8300 per c.mm. respectively. Blood taken for culture on Aug. 21 grew colonies of coagulase-positive *Staphylococcus aureus* by Aug. 23.

Treatment.—Sodium penicillin 30,000 units intramuscularly 3-hourly was administered from Aug. 22.

On Aug. 23 operation was undertaken for relief of pain and because of the alarming increase in the symptoms. The sternum was exposed through a midline incision, œdematous periosteum elevated over the manubrium, and the anterior cortex removed over a wide area by light gouging. Pus was evacuated and sent to the laboratory. The wound in the skin was closed, and a small rubber tube was inserted through a separate stab-wound for the administration of penicillin locally.

On culture, pus taken from the manubrium grew coagulase-positive *Staph. aureus*. Penicillin was continued. Relief from pain was dramatic, the wound healed by first intention, and a month later the patient was quite well again.

REFERENCES

Drews, H. (1910) Die akute Osteomyelitis des Brustbeins. *Parchim.*
Vaughan, R. T. (1918) *Surg. Clin. Chicago*, 2, 253.

"... No activity, however, whether of general practice, specialization, human relations or even medical journalism, should be allowed to settle into a status quo. Like an old mattress, it needs occasionally to be picked over, vacuum-cleaned and rebuilt, with the addition of some fresh horsehair or feathers."—*New Engl. J. Med.* March 6, 1952, p. 385.

Reviews of Books

Clinical Urography

An Atlas and Textbook of Roentgenologic Diagnosis. WILLIAM F. BRAASCH, M.D., emeritus consultant in urology, Mayo Clinic; JOHN L. EMMETT, M.D., consultant in urology, Mayo Clinic. Philadelphia and London: W. B. Saunders. 1951. Pp. 736. £6 5*s.*

THIS massive work from the Mayo Clinic is in every respect worthy of that great institution. It is the most comprehensive treatise yet published on the subject. More than 1300 films are reproduced, depicting a large number of variations of the normal, particularly of the pelvi-caliceal pattern.

It may be carping to find any faults here; but osteitis pubis seems to have been overlooked, and the section on urethrography includes no mention of the descending route or of the excellent technique developed by Stobbaerts, of Brussels. Language purists have told us that "orchiectomy" should be substituted for the more common "orchidectomy"; but here the word appears repeatedly as "orchectomy."

The relatively high cost of this book may keep it from many bookshelves; but it deserves a place in the library of every radiologist and urological surgeon.

Chronic Bronchitis

TREVOR H. HOWELL, M.R.C.P., physician, geriatric research unit, St. John's Hospital, Battersea; consulting physician, Bermondsey Medical Mission Hospital, London. London: Butterworth. 1951. Pp. 111. 17*s.* 6*d.*

THIS book is the outcome of careful clinical observation and research linked with the pathological background of the disease, and a wide knowledge of other publications. Dr. Howell's experience at a geriatric research unit and previously among the Chelsea pensioners has also equipped him well for the task of writing this monograph. In it are presented many valuable facts concerning chronic bronchitis—its types, symptoms, and physical signs together with complications and prognosis. It is, however, in the sphere of treatment that the book's practical value is greatest. The author has experimented with the commoner expectorant drugs and antispasmodics, and reaches definite conclusions about both. This pleasantly written monograph will be of service to both the general reader and the specialist.

Vitamins and Hormones

Vol. IX. Editors: ROBERT S. HARRIS, professor of biochemistry of nutrition, Massachusetts Institute of Technology, Cambridge, Mass.; KENNETH V. THIMANN, professor of plant physiology, Harvard University, Cambridge, Mass. New York: Academic Press Inc. Pp. 395. $8.

WE have come to expect a high standard from these annual collections of reviews, and the nine articles in this volume fulfil this expectation.

This year, as last, there is an article on vitamin B_{12}, but this time by two different authors (T. H. Jukes and E. L. R. Stokstad). Those who remember biotin only as something rather unreal, vaguely connected with egg-white, will enjoy the article by H. C. Lichstein, which sets out as clearly as these things can be set out the functions of this vitamin in the decarboxylase and deaminase systems. The extraordinary progress in intermediary metabolism which has been made possible by the use of radioactive elements is illustrated in an article by William Shive on "the functions of the B vitamins in the biosynthesis of purines and pyrimidines," and in another, by G. H. Twombly, on "the synthesis and metabolism of radioactively-labelled steroids." Radioactive steroids do not seem to concentrate, as iodine does, in the organ on which they exert their physiological effect; hence their use for localised radiotherapy seems unpromising at present.

L. D. Wright has contributed an article on "antimetabolites of nucleic acid metabolism," and Agnes F. Morgan one on "the effect of vitamin deficiencies on adrenocortical function," covering not only the well-known changes in the ascorbic-acid metabolism of the glands but their functional relations to thiamine, pantothenic acid, and riboflavine. R. G. Sprague summarises the effects of cortisone and A.C.T.H., and W. H. Fishman discusses the relation between œstrogens and enzyme activity. Most of the reviews deal with aspects which are increasingly important or are centres of interest at the moment. As in previous years, however, the less popular but no less promising subjects have not been neglected; and the last article, by M. H. F. Friedman, describes the discovery, assay, and exploration of urinary gastric secretory depressants—substances that must surely have a future in the treatment of some of the disorders of the stomach which are responsible for so many outpatient attendances.

These reviews will be found of great value for teaching and reference, and each concludes with a long list of the original papers quoted. The editors have decided to strengthen the board by including on it Prof. G. F. Marrian, F.R.S., of Edinburgh; and this move will be appreciated by workers on the eastern side of the Atlantic.

Rotgrünblindheit als Erlebnis

HEINZ AHLENSTIEL. Göttingen: Musterschmidt. 1951. Pp. 47. D.M. 4.80.

Dr. Ahlenstiel is himself colour-blind, suffering from that form of red-green blindness known as protanopia—the deficiency which also afflicted Dalton and which he too described at first hand. Dr. Ahlenstiel has not, as Dalton did, described his colour experiences with the idea of adding to the scientific knowledge of colour-vision. His book is largely written for others who may be colour-blind and is a practical attempt to help them (as well as those with normal vision) to understand their disability.

The discussion is based on Ostwald's colour system, and most of the book describes in detail what the hues of the Ostwald 24-colour circle look like to the red-green blind. A more scientific approach, based on some discussion of colour-vision theory, would have tightened the argument; but the book as it stands is well suited to readers without scientific knowledge or training, among whom most of those with defective colour-vision are to be found. One rather serious factual error may be noted: it is not true that the deuteranope has a lowered sensitivity to the green wave-lengths as the protanope has to the red: the confusions experienced by the deuteranope seem to be due to some fusion of the red and green mechanisms rather than to an absence of the green one.

Many colour defectives are uneasy about their disability (often to the extent of refusing to admit it), and any attempt to help them is welcome. At the same time the somewhat intense and self-pitying approach of this otherwise good book is perhaps not the most helpful.

Brain Metabolism and Cerebral Disorders

HAROLD E. HIMWICH, M.D., chief, clinical research branch, Medical Division U.S. Army Chemical Center, Maryland. London: *Baillière, Tindall, & Cox.* 1951. Pp. 451. 46*s.* 6*d.*

OF necessity Dr. Himwich deals with carbohydrate metabolism and its disturbances. His own distinguished career reflects the rapid growth of knowledge of the chemistry of brain function; and if the time has not yet come to write an account of the chemistry of neurological disease, it is ripe for an appraisal of its basis. In this impressive book are packed the facts of cerebral metabolism so far as research has gone, integrated with electrophysiology, pathology, therapeutics, and clinical observation. Dr. Himwich hopes that various parts of the book will be of use to "all those involved in the study of the brain, normal and abnormal," and as he includes by name neurosurgeons, pædiatricians, and psychologists, he had to make his base very wide. He defends it with a detailed bibliography of over 1000 references.

If the book is formidable to anyone other than a biochemist, at least it is in tune with its subject; and Dr. Himwich has shown skill in treating his specialty so lightly. The title of the first half is "Energetics," and in this he deals with the chemistry of carbohydrate breakdown, and its relation to cerebral blood changes and bodily physiology. He continues with an account of changes with hypoglycæmia, body growth, and pathological states. In the second part, "Patterns of Nervous Activity," he relates chemistry to other aspects of physiology in a chapter on the brain tissue itself (the somati division) and one on the autonomic division. These subj- wait on further research, which is discussed in a chapter prospects and problems of the future. Progress in this fiel is so rapid that this part of the book will have to be modifie and extended before long.

This is an important addition to neurological books reference.

Electro-encephalography in Clinical Practice

ROBERT S. SCHWAB, M.D., director of brain wave [illegible] tory, Massachusetts General Hospital. Philadelphia an London: W. B. Saunders. 1951. Pp. 195. 32*s.* 6*d.*

THIS is a first-rate little book for the clinician wh wants to know enough about electro-encephalograph to apply it intelligently to his problems. The evidence of electrical activity of the brain are so diverse that thei application to clinical work calls for a good deal of menta agility. To try to explain disorders of [illegible] in terms of disturbed brain structure is [illegible] but to relate them to electrophysiological disturbance brings in a host of new, unknown factors. Until he i disillusioned by the reports, and the records on whic they are based, the clinician may think that electro-encephalography will give him more reliable evidenc than that of the other methods he uses; whereas i really adds new facts which require very careful assessment. Dr. Schwab gives a balanced judgment of th contribution that the E.E.G. makes to neurology an psychiatry. He explains the tried techniques accurately with plenty of photographs and diagrams, and he show the results of these techniques, in records, clinica examples, and statistics. The value of the E.E.G. i epilepsy, organic neurology, and psychiatry, is intelligently discussed, and he provides a few well-chose references.

A Textbook of Gynæcology (6th ed. London: J. & A. Churchill. 1952. Pp. 672. 27*s.* 6*d.*).—*Mr. Wilfred Shaw's* book is always welcome, and here it is again, brought up to date. The title page carries the motto "omne tulit punctum" which (as those of us who have a dictionary of *quotations* to hand will remember) is the beginning of a passage from Horace, sometimes rendered: "He gains universal applause who mingles the useful with the agreeable, at once delighting and instructing the reader." The text punctiliously observes the recipe, and entitles Mr. Shaw to an enthusiastic receptio and an encore in a few years' time.

Hundert Jahre Augenspiegel (Leipzig: Georg Thieme. *1951. Pp. 68. D.M. 6).—To mark the centenary of the* invention of the ophthalmoscope by Helmholtz, the ophthalmologists of the German Democratic Republic held a special commemoration meeting on Dec. 10, 1950; and the five addresses then delivered are published in this memorial volume. An account of the Helmholtz ophthalmoscope is given by W. Comberg; and subsequent developments are discussed by K. Velhagen. G. Lenz gives an account of photography of the fundus and the lens as an incidental development. The highlights in the growth of *knowledge in ophthalmology* by means of ophthalmoscopy are brought out by H. Gasteiger. The concluding address, by D. Schulte, deals with the correlation of fundus and histological appearances. These addresses give a balanced historical picture, even if they contain little new.

The Tissues of the Body (3rd ed. Oxford: Clarendon Press. 1952. *Pp.* 407. 30*s.*).—*This stimulating textbook* by Prof. W. E. Le Gros Clark, F.R.S., has had to catch up with six *years of passionate* activity among the anatomists. At one time these enthusiasts seemed to be reaching the *limits of* their subject, anyhow in human anatomy, where there was little left to describe; but first microscopy, and later tissue culture, opened new realms; and now electrical, biochemical, and endocrinological studies are adding fast to *our* understanding of function and structure. Professor Le Gros Clark has always believed *in giving students preliminary* glimpses of the view from higher up the mountain, and this new edition, like its predecessors, shows them some of the prospects now unfolding before research scientists perched aloft. Such glimpses nourish the intellect as powerfully as they stir the imagination; they are the good teacher's *justification*, and his bait.

THE LANCET

LONDON: SATURDAY, APRIL 12, 1952

The Notification of Tuberculosis

The main purposes of notifying infectious diseases are to mobilise the resources of the health authority and hospital service on the patient's behalf; to apply control measures without delay for the protection of the community; and to provide data for the planning of national policies of prevention and control. Early ascertainment is often as vital in tuberculosis as in more obviously urgent conditions, such as meningococcal meningitis or poliomyelitis; for the lives of other members of the patient's household may depend on how quickly he is isolated or his infectivity controlled. Moreover, as soon as we have a specific drug applicable to early cases the value of early diagnosis and immediate treatment will be greatly enhanced. Recognised and universally operated standards for notification are essential to an understanding of the epidemiology of tuberculosis and intelligent plans for its control. "Data are of little use if some reflect all cases including suspects, while others show only active cases with positive bacterial findings."[1] In the United States, the importance of this proposition led a joint meeting of the State tuberculosis control officers and State sanatoria directors to set up a committee, which has proposed the following criteria [1]:

To be reported:

1. Cases with tubercle bacilli demonstrated.
2. Cases with other significant evidence, even though bacteriological proof has not yet been demonstrated, such as: (*a*) Chest X-ray shadows characteristic of active tuberculosis (soft infiltrate, cavity, &c.); (*b*) unexplained pleurisy with effusion; or (*c*) clinically active extrapulmonary tuberculosis (meningeal, bone, kidney, &c.).

May be reported:

1. Cases of pulmonary fibrosis and nodulation more than minimal in extent, presumably of tuberculous origin.
2. Cases with a record of active disease or previous treatment within the past five years.
3. Cases with X-ray evidence of collapse therapy or resection for tuberculosis.
4. Active primary pulmonary tuberculosis cases.

Not to be reported:

1. Chest X-ray film revealing fibrous lesions, minimal in extent, without history or symptoms. (This includes fine linear strands; discrete, hard nodules; and apical-pleural scars.)
2. Positive tuberculin reaction only.
3. Pulmonary calcification, including healed primary tuberculosis.
4. Healed extrapulmonary tuberculosis.

In this country the notification of tuberculosis has a long history. At the end of the 19th century local authorities began to introduce measures for voluntary or compulsory notification. In 1909 the Local Government Board made a cautious gesture by instituting compulsory notification of pulmonary tuberculosis in poor-law cases; this was extended to hospital cases in 1911, and to the general population in 1912. In 1913 compulsory notification was applied to all forms of the disease. From that time onwards the annual reports of the chief medical officer of the central authority contain an interesting series of comments. In 1913–14, for example, he observes that notification should be the occasion for discovering other cases in the home of the notified person, for ascertaining the patient's working and social environment, and for dealing with conditions which favour the spread of infection. The importance of the search for the primary case is explained. In addition, at follow-up visits the health visitor should impress the need for separate sleeping-quarters for the patient, and be on the watch for contacts who are in failing health. In the following year it is noted sadly that some medical practitioners fail to notify, because they do not appreciate that investigation is likely to uncover a source of infection or to reveal bad housing conditions. As time goes on the comments on incomplete notification become frequent, and three main reasons for failure are mentioned: (1) delay by the patient in seeking advice; (2) uncertainty about the diagnosis; and (3) the belief that the patient had previously been notified by another practitioner. From the ratio of deaths to notifications, the number of cases not reported till after death, and the high proportion of cases not notified until shortly before death, it is clear that up to about 1939 notification was still very incomplete. The report for the years 1939–45, however, notes a considerable improvement in notifications, accompanied by an increase in new cases under supervision and treatment. There is no doubt that in recent years notification has become steadily more complete. Partly, no doubt, this is because the tuberculosis services have improved; for it is now clearer than ever that notification is followed by useful action. Of the other factors accounting for the improvement perhaps the most important are the greater concentration on tuberculosis as a part of clinical medicine, education of the public in the idea of tuberculosis as a disease responding to skilled treatment, and more effective social and economic provision for the tuberculous patient and his family.

Improved notification has its own dangers—over-reporting, for example, could be almost as damaging as under-reporting—and clearly we need more precise criteria. In the first place, statistics for different areas should be comparable with each other. If in some areas minimal and inactive lesions are notified after mass-radiographic examination, and pædiatricians are zealous in reporting positive skin tests, then the figures will become chaotic. One effective remedy for this is some form of intimation, short of formal notification, which would enable a practitioner to give notice of cases under suspicion, reserving notification for patients in whom the diagnosis has been confirmed after consultation with a chest physician. But though this idea has had authoritative support, it has not found official favour. A standard procedure is also needed for removing a patient's name from the register. At present a chest physician may take off the register the name of a patient whose lesion has been

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[1] American Trudeau Society. *Amer. Rev. Tuberc.* 1951, 64, 579.

"arrested" for five years; but he is not obliged to do so, and the practice varies. Some physicians prefer to leave names on the register for a longer period, so that they can continue to exercise at least some supervision. Furthermore, notification may create personal difficulties for the patient, so that the doctor is reluctant to make a formal report. For example a youngster of 16 with a healed primary lesion may be rejected for National Service because his name is on the register; and a child with a similar lesion may have more difficulty than other children in getting a place in a convalescent home. There may be difficulty, too, over admission to a university or to a business or academic appointment; and from time to time there are instances—unfortunately becoming commoner—of fellow-workmen resisting the return of a man who is still under supervision for tuberculosis. Removal from the register should be a formal process which, so to speak, erases the mark.

The Vestibular Organ

THE early experiments on the vestibular organ consisted chiefly in extirpation of portions of the organ, sometimes accompanied by brain section at various levels, followed by observation of the animal's spontaneous and induced behaviour. Investigations in this field were reviewed in these columns some years ago by MAXWELL ELLIS[1]; and since then, though no revolutionary discoveries have been made, experimental techniques have been greatly simplified. The place of decerebrate animals, deprived of one or both labyrinths, has been taken by contemplative patients gently oscillated in swings or rotated in chairs. Ears are no longer syringed with ice-cold water; temperatures only slightly removed from that of the body seem to suffice.[2] Experiments conducted in so calm an atmosphere, and in conditions so nearly normal, may be expected to give more consistent and reliable results, and a more accurate picture of the function of the vestibular organ.

Prof. L. W. K. JONGKEES[3, 4] has lately given an account of some of these modern methods, which he and his associates have been developing in Utrecht. Three types of apparatus have been evolved: the horizontal swing, which is a platform, suspended from all four corners by parallel ropes of equal length, and moving in a horizontal plane; a second horizontal platform, pivoted at the centre and revolving as a turn-table; and a chair mounted to rotate about a vertical axis. A person placed on these platforms or in the chair can be subjected to angular or linear accelerations, and a simple mechanism measures the stimulus applied. Such stimuli are within the bounds of those encountered in ordinary life.

The stimulus for the otolith organs is probably linear acceleration; and this conception has been investigated with the horizontal swing. It was at one time believed that the different parts of the labyrinth react reflexly, either to movements or to a changed position of the head in space—the so-called dynamic or static stimuli. Any movement, however, must always be the resultant of gravity and of whatever other force is being brought into play; the actual stimuli to the otolith organ are the acceleration and deceleration at the start and end of the movement. JONGKEES found that with the horizontal swing the direction of the acceleration given to the swing and of the acceleration of gravity form a parallelogram of accelerations with a calculable direction; and normal subjects oscillated on the swing invariably confirmed this by their sensations. Thus, theoretically, if the patient is swinging head first he would feel that he was tilting backwards; and in fact this is the sensation he does perceive. Vice versa, when the swing is moving feet first he feels that he is tilting forward. It should be possible to place a normal person on the horizontal swing in such a position, and subject him to such a force, that the direction finds the "blind spot" of the labyrinth—that is, the position in which no otolith is in contact with its layer. This is found to be true in practice: the subject retains no sensation at all of his position in space, despite intact proprioceptive and skin reflexes.

Such experiments convincingly demonstrate that the vestibule is the organ of sense for the perception of linear acceleration.

JONGKEES states that some observations previously thought to indicate vestibular organ function—for instance, vertigo—really indicate an abnormal reaction. Vertigo is due to unphysiological stimulation of the organ, and possibly derives from the vegetative nervous system. He classifies nystagmus, past-pointing, and rombergism in the same way. Nystagmus, however, is an extreme degree of counter-rotation of the eyes; and this is the normal reflex from the vestibule, being the attempt of the organism to keep the moving world in focus; if not unduly severe, it can be used as a measure of vestibular stimulation. JONGKEES contends that the Barany method of rotation is too violent: it not only gives unphysiological results but may actually damage the labyrinth. Moreover, the stimuli applied by the initial acceleration and final deceleration neutralise one another. He therefore rotates the subject gently at a constant speed and studies the deceleration effect when the rotation is suddenly stopped. He notes the duration of the after-nystagmus and of the continuing sensation of rotation; this sensation always ceases before the nystagmus. In addition, these durations can be plotted against the stimulus (expressed in degrees per second of angular velocity) on a logarithmic scale, and JONGKEES calls the resulting graph a "cupulogram." Caloric tests give information about individual canals; cupulograms illustrate the physiological properties of the whole vestibular system—the labyrinth and its neural connections. In many people a directional preponderance is normal: nystagmus lasts longer after stimuli in one direction than after stimuli in the other direction. Directional preponderance of this kind is also found after damage by streptomycin, and if the preponderance is strong enough spontaneous nystagmus occurs; but this may soon disappear, whereas curves of directional preponderance persist. As healing progresses, however, the two lines approach and finally coincide, and the final graph is exactly midway between those previously obtained by clockwise and anti-clockwise rotation of the patient. In two other kinds of directional preponderance the graphs diverge or intersect. This is often so with peripheral disturbance—for example, in fenestration cases. Such curves are reminiscent of those obtained by loudness-recruitment tests. It is well known that destruction of one labyrinth is, after a time, attended by no detectable

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1. Ellis, M. *Lancet*, 1940, ii, 371.
2. Fitzgerald, G., Hallpike, C. S. *Brain*, 1942, 65, 115.
3. *Proc. R. Soc. Med.* 1952, 45, 127.
4. Lecture, Institute of Otology and Laryngology, London, Dec. 8, 1951.

isability. In such cases the cupulograms, too, ltimately become normal, whereas the Barany otation test reveals shortening of the after-effects. This perhaps indicates that cupulometry is a more "functional" test, and the Barany test a "burdening" one. In other words, the organism can be erved by one labyrinth for all normal purposes, but not when a heavy burden, in the shape of extrardinary stimulation, is laid on it. The fact that n normal subjects cupulograms obtained after a Barany test are always abnormal, and may not return o normal for some weeks, supports the view that this est is itself traumatic.

The vestibular apparatus as a whole can be regarded s the proprioceptive organ of the head, and vertigo s the impression in consciousness of the body's attempt o keep the head in normal relation with the outside world. Thus vertigo may result from unusual and undue stimulation, or from a derangement of the vestibular apparatus. Sir **Charles Symonds**[5] has enumerated a great variety of stimuli, circumstances, and esions in which vertigo is prominent; but he has also ncountered gross examples which defy such classificaion. At the same meeting Dr. C. S. **Hallpike** and Miss M. R. **Dix** described their work in this field. After studying a number of cases of vertigo they defined a clinical entity, separate from Ménière's disease, consisting in paroxysmal vertigo with no deafness and no tinnitus. Tests of hearing, including audiometry, reveal no significant impairment of cochlea function, whereas the caloric tests disclose gross derangement of vestibular function. The end-organ is not involved or at any rate not irreversibly, since in some cases subsequent caloric tests are normal. Focal infection is often associated with this syndrome, which may be due to a toxic lesion of the vestibular neurone—perhaps of the nuclei. Although the vertiginous attacks are often severe, the disease runs a benign course, sometimes resolving completely; it has never yet been observed to involve other organs or to cause death. **Barany**[6] described yet another variety of equilibrial disorder, which is less common but of equal interest: sudden head movements cause almost immediate vertigo associated with nystagmus. This disorder, which he named positional nystagmus, also runs a benign course. **Barany** ascribed it to a lesion of the otolith organ; and **Hallpike** and **Dix**, by carefully reproducing the causative movement and estimating the canal function by caloric tests, have found further evidence for this view. However, in a paper read to the American Otorhinolaryngological Association, **Lindsay**[7] described several varieties of positional nystagmus and contended that some are produced centrally as well as peripherally. In cases of cerebral tumour or other space-occupying lesions, variations in pressure during changes in posture might affect the vestibular nuclei, or the cerebellar connections. He quoted **Nylen**'s[8] findings of some form of positional nystagmus in 279 out of 673 cases of brain tumour—69% of subtentorial and 26% of supratentorial tumours. Among possible causes of positional nystagmus **Nylen**[9] also included transitory central vascular changes during allergic or toxic disturbances. In the discussion of **Lindsay**'s paper, **Shuster**[10] remarked that he had rarely found positional nystagmus in verified cases of brain tumour and believed it nearly always originated peripherally, probably as a result of a toxic focus. The proper treatment of vestibular vertigo must depend on separating these groups from Ménière's disease, not alone because of their benign natural history, but also because with them cochlea function is undamaged.

This advance in so difficult a branch of medicine is due to the correlation of clinical observation with increasing knowledge of vestibular function, which in turn derives from experiments ingeniously conceived and performed, yet simple and based on sound physiological principles.

Annotations

MORE MANURE

The passionate imaginations of the "muck and magic" school of agriculturists have given rise, by contrecoup, to some prejudice among those farmers who leaven tradition and experience with the teaching of the soil chemists. But it may soon be impossible for this country to buy great quantities of nitrogen, phosphorus, and potassium from Algeria, Chile, and the South Seas, and we shall be forced to consider the wastefulness of allowing so much of these essential elements to run away down the sewers. In Great Britain the practical and personal difficulties of handling such offensive matter as human excreta have led to its virtual disuse as manure; but these objections can probably be overcome by composting. This process, though accepted as normal practice by most gardeners, has not yet been applied to the production of large quantities of manure for agriculture, and the potential advantages of its use by farmers were examined by Mr. J. C. Wylie, county engineer of Dumfries, in an address to the Royal Society of Arts on March 12. Mr. Wylie commended the compost-heap not only as a source of valuable organic manure, but also as a means of refuse disposal with hygienic advantages over the usual method of controlled tipping, which often produces "offensive, vermin-ridden dumps of putrefying wastes."

To be, and continue to be, fertile the soil must contain a proportion of humus, a substance seldom defined but essentially what remains of organised vegetable matter after putrefactive bacteria have done their worst. If sewage sludge is added to domestic or industrial refuse, or to vegetable matter grown for the purpose, fermentation ensues, heat is generated, and the result is a compost of humus rich not only in the major essential elements but also in those "trace elements" whose absence or superfluity produces such curious biological puzzles. If the farmer has made less use of this process in the past than the gardener, it is because he has often been self-sufficient in manure and has lacked a surplus of vegetable substrate. To obtain humus it has been quicker and cheaper—and quite probably as effective—to plough in a "green manure" crop or the straw left by the combine harvester. But, as Mr. Wylie pointed out, the farmer gets less farm-made manure now that the livestock population is falling; and this at a time when increased mechanisation and chemical fertilisers make intensive cropping possible. There are thousands of acres which would be the better for the regular application of a rich compost, and for this reason his account of the large-scale composting of wastes with sewage sludge undertaken in the county of Dumfries is a matter of wide interest. This scheme is beyond the stage of experiment and the finished product sells at 50s. a ton, which compares none too badly with the price of farmyard manure. Spreading manure is one of the costliest processes on the farm, and if this compost is of a texture fine enough to be applied like a chemical fertiliser the gain will be considerable.

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[5] Section of Otology, Royal Society of Medicine; Jan. 7, 1952.
[6] Barany, R. *Acta otolaryng., Stockh.* 1921, 2, 434.
[7] Lindsay, J. R. *Ann. Otol., &c., St. Louis*, 1951, 60, 1134.
[8] Nylen, C. O. *Acta otolaryng., Stockh.* 1939, suppl. 33.
[9] Nylen, C. O. *J. Laryng.* 1950, 64, 295.
[10] Shuster, B. H. *Ann. Otol., &c., St. Louis*, 1951, 60, 1151.

As citizens we must praise this example of sound economy. As doctors we would suggest that those responsible make certain that the use of human excreta brings no risk of spreading infection. Sewage sludge may, and often does, contain not only the organisms responsible for typhoid and dysentery, but also tubercle bacilli. The high incidence of enteric infections in China has been attributed to the use of human fæces to fertilise the vegetable gardens. Composting on a small scale and in expert hands is said to engender enough heat to destroy bacteria, but we are not aware of specific experiments which show that composting on an industrial scale yields a product free from pathogenic organisms. The danger may easily be exaggerated: much cow dung must surely contain *Salmonella dublin*, and tannery wastes used as fertilisers often teem with anthrax bacilli; yet we have no proof of human infection from either source. But it would be regrettable if a sound and sensible plan for the utilisation of waste products earned a bad name in its infancy by initiating an epidemic of enteric fever. Proof of innocence presents no technical difficulties and should be established.

PROTECTION OF SCHOOL-CHILDREN AGAINST TUBERCULOSIS

SOME time ago the Joint Tuberculosis Council made recommendations to the Minister of Health regarding the protection of organised groups of children against the risk of infection by adults with tuberculosis; and the Ministry of Education has now issued a circular to education authorities and others responsible for groups of children concerning ways in which some of these recommendations may be implemented. For the most part the circular advises on methods requiring the voluntary coöperation of teachers and others dealing with children, but in two important particulars the recommendations of the Joint Tuberculosis Council are to be made compulsory. Firstly, after the summer of 1953 every person becoming a teacher in a school maintained by a local education authority will be required to have their chest examined radiographically as part of their medical examination. Secondly, teachers resuming duty after absence due to tuberculosis will be required to produce more frequent medical certificates over a longer period than at present, and the certificates will have to be based on bacteriological and radiological as well as clinical examinations.

Compulsory radiographic examination on entry will detect some cases of active tuberculosis; and in their own interest, as well as that of others, these patients will require treatment. The examination will also bring to light a number of cases of healed, healing, and questionably active disease; and such patients presumably will have to furnish certificates comparable with those required from teachers returning to duty after treatment for tuberculosis. To exclude from teaching all found to have small shadows or shadows of healed lesions would be an unreasonable waste of trained people, and unfair to the individuals concerned; but there is no reason why they should not be required to accept the strict supervision specified for the teacher who has had active disease which has responded to treatment. Indeed, such supervision is the best possible course in their own interest.

Compulsion is not to be used for groups other than teachers, but each authority is advised to organise a procedure as nearly as possible in line with that required for teachers. One recommendation of the Joint Tuberculosis Council is not fully implemented—namely, annua re-examination of all in the teaching profession. Th circular states that there are not sufficient radiographi resources for this, but recommends that special arrangements be made locally with mass-radiography units fo routine examination of teachers; this places a considerable responsibility on individual teachers to voluntee for examination. A final brief paragraph suggests tha the local health authority should be asked to undertak a special investigation if an undue incidence of tuberculosis is found in a school or class. The recent investigation by Bevan et al.[1] suggests how this task might b approached. Under these conditions, tuberculin testin of the children is certainly most useful; and it ma help to identify the members of the staff who are th most likely sources, or suggest a source outside th school.

FEEDING RISKS IN EARLY LIFE

FOR most people the hazards of the first year of lif are exceeded only by the hazards of the last. Even i countries where welfare services are well developed an the level of maternal knowledge is reasonably high, death may range from 30 to 50 per 1000 children in the firs year of life, compared with only 2 or 3 per 1000 of thos aged 1–4 years. In backward countries the mortalit may be as high as 100–250 per 1000 in the first year against 20–80 in the 1–4 age-group. The breast-fe child, of course, stands the best chance of avoiding feedin disorders, for he can count on appropriate, protective and hygienic food, which he does not seem to fin monotonous. His feeding troubles, if any, will com later, when he is weaned; for now he depends not on th apposite wisdom of Nature but on the social customs marketing opportunities, and gumption of his mother—uncertain quantities in every part of the world. I countries where cow's milk is plentiful he has a good chance of surviving the transition to the mixed famil diet without undue strain on his digestive organs; but in some primitive African communities the mothe forces starchy pap on her 2–3 months' old child, from a cupped unwashed hand. Between birth and weaning every child has to develop the necessary enzymes for dealing with starch, a process taking five months or more. The digestion assaulted with a heavy load of starch at earlier ages may be prejudiced for life; not that this need be long, for the feeding method used is liable to introduce gastro-intestinal infection, and between indigestion, infection, and infestation with tropical parasites, it is a tough baby who survives. Moreover, in many countries, as Mr. F. Le Gros Clark[2] points out, cow's, or even goat's, milk is exceedingly scarce, and the child is unlikely to get any. In such countries breast-feeding is often continued until the end of the second or third year or even later, and this practice brings its own hazards; for the child of 2 receiving an almost unsupplemented diet of breast-milk soon becomes malnourished and may develop rickets.

Mr. Le Gros Clark takes the view that even if most of the risks of infection and infestation could be eliminated, we should still have, in the case of children between 1 and 3 years old, to deal with a special nutritional problem. A child over 3 can usually adapt himself to rather a poor diet, provided it contains the necessary minimum of protein, minerals, and vitamins, and provided the calories are just sufficient. If he has to go through a hungry season, and survives it, he is usually able to recover normal growth and physical conformation though he may end up slight in build. But it is not at all certain that this holds for the child between 1 and 3. In countries where milk is plentiful it has been accepted

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1. Bevan, R. T., Bray, P. T., Hanly, J. F. *Brit. med. J.* 1951, ii, 828.
2. The Feeding of Preschool Children. London: National Society of Children's Nurseries, 45, Russell Square, W.C.1. *1952.* Pp. 51. 1s. 6*d.*

is the "natural" food of the child, and if the parents cannot provide it the community generally does. Some communities lacking milk may have devised effective substitutes, but if so, Mr. Le Gros Clark says, we know ittle about them; though he does mention that some of he peoples of Central America wean their children on a diet of bean paste and maize meal soaked in limewater, which must provide most of the protein, calcium, and B vitamins needed. However, the obvious solution is for the countries well supplied with cow's milk to export it in the dried form to the peoples who lack it. In theory, supplies of dried skim-milk from the main dairying countries of the world could be greatly increased, and though the cost would be substantial he believes that dried milk should be viewed as a necessary reservoir for the feeding of young children, and that besides exporting it to needy communities we should be teaching them to use it properly. In a thoroughly sane world, he remarks, this is what would happen. But it is quite as likely to happen in an insane world—the ability to do two opposite things at once being a symptom of our insanity.

DISTAL MYOPATHY

In 1902 Sir William Gowers[1] lectured at the National Hospital, London, on a distal type of myopathy. Since then, however, the existence of a myopathy affecting predominantly the distal parts of the limbs has been disputed, and it has been suggested[2,3] that the patient described by Gowers possibly had myotonic dystrophy. Welander[4] has now demonstrated, however, that a distal type of myopathy does in fact exist, and that in Sweden it is not extremely rare. In the neurological department of the Serafimer Hospital, Stockholm, 23 such cases were seen between 1939 and 1948; and, starting with these and 55 other cases reported to him from various sources as probands, Welander discovered 171 "secondary" cases. He bases his account on his personal examination of these 249 patients.

The disease, like other types of myopathy, is heredofamilial; a dominant inheritance is usual, and in six families he traced the disorder through four generations. In typical cases symptoms start between the ages of 40 and 60, men being more commonly affected than women; and the muscles first affected are usually the small muscles of the hand and the long extensors of the fingers and thumb, one hand often being involved before the other. In the course of several years similar wasting and weakness begins in the periphery of the legs, involving the intrinsic muscles of the feet and the extensors of the toes and ankles. The wasting and weakness of the affected muscles increase very slowly over the years, and in advanced cases the long flexors of the fingers and toes may be slightly involved. In the early stages the tendon reflexes are unchanged, but later the ankle-jerks may disappear. Fibrillation is not a feature of the disease, and there are no sensory changes. Welander describes 9 cases in his series as "grossly atypical." Apparently in each of these both sides of the family were affected; the patients were probably homozygotes to the relevant gene, which may account for the rather unusual features. In this group the legs were predominantly affected; flexor as well as extensor muscles were involved, and muscles above the knees and elbows became weak (which did not occur in the typical heterozygous cases); and the disease was usually more rapidly progressive, with complete incapacity in 10–15 years.

Full post-mortem examinations were carried out in 3 cases where the patients died of other causes; and no abnormalities were found in the central nervous system, the spinal-root ganglia, or the peripheral nerves. Muscle biopsies from 26 other patients showed the type of change regarded as characterising the myopathies; an important point was the normal appearance of the intramuscular nerve-trunks. Electromyography was done by Kugelberg in 71 of the patients, with findings of the type which he has previously described[5,6] as typical of myopathic degeneration.

This thorough study leaves no doubt that a distal type of myopathy exists; and the disease most likely to be confused with it is the peroneal muscular atrophy of Charcot and Marie[7] and of Tooth.[8] In peroneal muscular atrophy the muscle wasting is secondary to changes in the peripheral nerves; the disease usually appears at a much earlier age than does distal myopathy; pes cavus is common; the ankle-jerks disappear at an early stage; and initial involvement of the hands and forearms is most unusual, the peronei and extensors of the toes and ankles being involved first in the great majority of cases. In addition a slight sensory impairment, in particular of appreciation of vibration, is common (this was found in 15 out of 16 patients over the age of 15 examined by Welander), while occasionally the sensory disturbance is much more extensive.[9] Welander concludes that differentiation of these two heredofamilial disorders should not be difficult; other conditions which superficially resemble distal myopathy—in particular motor-neurone disease and myotonic dystrophy—should present no great diagnostic difficulty.

EXPLAINING OURSELVES

ONLY the wise can afford to be simple; the rest of us must cloak our deficiencies in the long words of knowledge. Simplifying a technical subject calls for two assets: first, clear vision of the whole field, together with the sense of perspective that distinguishes its salient features; and secondly a fluent vocabulary, so that the picture can be translated from technical idiom into ordinary English. These two virtues are rarely conjugated; and perhaps the outstanding exponent of such a happy association was the late Sir James Jeans, who was not only thoroughly at home in the universe but was able to tell children so in words that gripped their imagination. In medicine we could do with a Jeans or two; for, whether we admit it or not, we commonly obscure our knowledge in a fog of technical terms. By this device we can deceive not only ourselves but our hearers; and examiners could profitably include in every paper at least one question that had to be answered in simple phrases. In the examination for the D.P.M., for example, "Defend the analytical method in 600 words fit for a layman" would be both a fair and a searching question; for the advantage of those with good judgment would shine through their essays.

Impressed, perhaps, by our ineptitude at telling what we know, the late Dr. Harry Roberts gathered a team of experts, and together they wrote *Everyman in Health and in Sickness*.[10] Here was set out what the intelligent layman might want to learn of anatomy and physiology, of how to keep fit, and of how to combat minor maladies and deal with emergencies, as well as much useful information on such matters as parenthood and birth-control, occupational *problems*, and the conduct of life in old age. When it was published in 1935, this book became a standard work of its sort. In revising the volume, which has now been reissued, Dr. Margaret Jackson has sought to bring each chapter up to date; and she has also added some of her own. One may regret the pictures of naked gymnasts on the dust-cover; but these should not deter the reader from the pages beyond. The book neither evades nor patronises; and the doctor who reads it will find that its fresh words bring fresh light to his ideas of human life and activity, as well as enabling him to impart those ideas to patients in need of information.

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[1] Gowers, W. R. *Brit. med. J.* 1902, ii, 89.

[2] Wilson, S. A. K. Neurology. London, 1940; vol. 2, p. 982.

[3] Critchley, M. Sir William Gowers. London, 1949.

[4] Welander, L. *Acta med. scand.* 1951, suppl. 265.

[5] Kugelberg, E. *J. Neurol. Neurosurg. Psychiat.* 1947, 10, 122.

[6] Kugelberg, E. *Ibid*, 1949, 12, 129.

[7] Charcot, J. M., Marie, P. *Rev. Médecine*, 1886, 6, 97.

[8] Tooth, H. H. The peroneal type of progressive muscular atrophy. Thesis for doctorate of medicine in the University of Cambridge. 1886.

[9] England, A. C., Denny-Brown, D. *Arch. Neurol. Psychiat.* 1952, 67, 1.

[10] Everyman in Health and in Sickness. By Dr. HARRY ROBERTS; revised by Dr. MARGARET JACKSON. London: J. M. Dent & Sons. 1952. Pp. 742. 25*s.*

JOINT-STRAIN IN SLEEP

As long as we are up and doing, our joints are kept nicely in the true, not only by their ligaments but also by the tone of neighbouring muscles. Under deep anæsthesia, especially in the curarised patient, muscle tone is diminished or lost, and the task of holding the joint in position falls largely or entirely on the ligaments. In such circumstances a poorly supported joint will be under a strain, the ligaments may give a little, and neighbouring nerves or other structures may be compressed by the shifting bones. This is what can happen, as we know, when a curarised patient in the Trendelenburg position has his arm abducted, extended, and externally rotated by the anæsthetist: the shoulder-joint becomes mildly subluxated, and the head of the humerus, forced anteriorly by the weight of the arm, stretches the brachial plexus and causes a brachial palsy.[1]

It does not seem impossible that in deep sleep a similar loss of tone in the muscles may leave the joints undefended; and that a careless and hearty sleeper may so dispose himself as to put some of them—particularly the small joints of the spine and the costovertebral joints—under undue strain. This, at all events, is the contention of Dr. James McDonnell,[2] who has studied the sleep posture of patients with various unexplained pains. We can all bear out his opinion to some extent: for who has not slept with the pillow awry and wakened with "a crick in the neck"? Dr. McDonnell submits that the proper way to sleep is with the vertebræ in a reasonably straight horizontal line, corresponding with the vertical line of the waking man. There is only one way to achieve this—namely, by lying on the side with the head resting on a pillow which fits well in under the neck but is not so high as to bring the cervical vertebræ out of the horizontal plane of the rest of the spine. Dr. McDonnell thus endorses the practice of those skilled and experienced sleepers who lie first on the back, seize the two lower corners of the pillow and pull them down over the shoulders, and then roll cannily on to the side with the head and neck in the mould or forme thus contrived for them. It is a mistake, as he points out, to *sleep* on the back, because this position takes no account of the anteroposterior curves of the spine (or, for that matter, of the natural position of the knee-joint, which keenly resents overextension). Unless a pillow is placed under the knees, so that the hip-joints are partly flexed, the sleeper on his back is bound to suffer some degree of lumbosacral strain. Those who sleep on the front are in no better case, for an obstinate habit of breathing obliges them to turn the head to one side or the other, and so to twist their necks.

The side-sleeper, then, has it; though even he can make mistakes. If the spine is to be supported in the horizontal plane, the pelvis and the shoulder-girdle must provide fixed supports of about the same height. The pelvis can be anchored by bringing the upper leg forward across the lower leg, and letting the knee, conveniently flexed, rest on the bed. The shoulder-girdle is fixed by bringing the upper shoulder and arm forward, and allowing the elbow and forearm to rest on the bed—or, as Dr. McDonnell, mindful of the spreading form, observes—as near the bed as the build of the sleeper allows.

Those who sleep carelessly—with the head too high, the neck unsupported, the upper shoulder falling back, the upper knee behind the lower, or on their backs or on their faces—put the spine to inconvenience, crowding the vertebræ at one edge and fanning them at the other, and placing strains of comparable kinds on the costovertebral joints. While the subject is dropping asleep he probably feels no discomfort, because his muscles are protecting his joints and ligaments by countering the effects of gravity; but the deeper his slumber the less his muscles can do for him; and these little joints, Dr. McDonnell believes, suffer "passive trauma," which declares itself later in intercostal neuralgia, "rheumatic" pains, and other undefined aches interpreted as abdominal disorders, cardiac pains, pleurodynia, and the like. The joint responsible for tenderness can be checked, he says, by placing the patient on a couch in the lateral position, and exerting forward pressure on the neck of each rib in turn. Thus tenderness in the rectus abdominis muscle at the site of emergence of the 8th intercostal nerve is associated, he finds, with tenderness in the region of the [illegible] vertebral joint. He has had good [illegible] many of these obscure aches and pains by manipulations designed to move the costovertebral joints about, and stretch the spine. But, as he honestly admits, he can offer no scientific analysis of the action of these manipulative movements: he can only say they work; and he is anxious, moreover, that others should check his results.

GROWTH HORMONE AS AN AID IN POSTOPERATIVE NUTRITION

THE extensive use of antibiotics and generous blood-transfusions, the improvements in anæsthesia, "early rising" after operation, and closer attention to the patient's preoperative and postoperative nutrition have changed the face of surgery almost beyond recognition in the last ten years. Though surgeons in all fields have become bolder since the war there has been a fall rather than a rise in operative mortality and the incidence of most postoperative complications. Comparable pre-war and post-war figures for the duration of convalescence after some single surgical procedure are hard to come by, but the surgical patients of today seem to be out of bed, walking round the ward, and back to work in next to no time.

Judging from Keeton's[1] studies of convalescence, nutritional management, especially in the immediate postoperative period, is one of the most important factors in restoring the patient's fitness after surgery. In 1935 Cuthbertson[2] began a series of studies of the effects of injury on plasma protein in animals. This work eventually led to the investigations of Browne and others[3] in man, which showed that considerable quantities of tissue protein may be broken down for days or even weeks after trauma of various kinds, including surgery. The nitrogenous fragments and other end-products of protein katabolism are excreted in the urine, and in consequence the patient is in negative nitrogen balance. Postoperative katabolism is now ascribed to the direct action of circulating compound F (17-hydroxycorticosterone) on body proteins. The liberation of this substance by the adrenal gland into the blood-stream is thought to be due to the successive stimulation of the hypothalamus (by adrenaline), the anterior pituitary

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1. *Lancet*, 1950, i, 121.
2. *Brit. J. phys. Med. indust. Hyg.* 1946, 9, 46; *Rheumatism*, 1948, 4, 238.

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1. Keeton, R. W., Cole, W. H., Mitchell, H. H., Dynlewicz, J. M., Kulasavage, R. J., Abramson, D. I., Gephardt, M. D., Lavers, G. D., Sapienza, A. R., Presley, S. J., Russell, C. E., Calloway, N. O. *Trans. Ass. Amer. Phys.* 1915, 51, 129.
2. Cuthbertson, D. P., Tompsett, S. L. *Brit. J. exp. Path.* 1935, 16, 471.
3. Browne, J. S. L., Schenker, V., Venning, E. H. *Trans. Ass. Amer. Phys.* 1946, 59, 235.

(by hypothalamic excitatory neurones), and the adrenal cortex (by A.C.T.H.). These hormonal activities, set going by an operation, lead to loss of weight and strength and sometimes to delay in wound-healing. Browne et al. in Montreal, and Taylor and colleagues[4] at Harvard, were among the first to establish the practicability of compensating for this protein breakdown by raising the intake of protein and calories to well above the generally accepted levels.

By 1945 the value of postoperative hyperalimentation was recognised in both military and civil hospitals.[5] "Stuffing" the patient with high-protein foods is expensive and calls for constant supervision and care. It has to be done when the patient's appetite has gone and is therefore a common source of friction between nurse, patient, and surgeon. There is clearly a need for some simple method of blocking postoperative nitrogen loss, and some work by Selye[6] might help. He has shown in rats that daily injections of pituitary somatotropic hormone (S.T.H.), otherwise known as growth hormone, can prevent the cessation of growth, loss of weight, and involution of thymic and splenic tissue which otherwise occur when multiple abscesses are produced by subcutaneous injections of sterile turpentine. If a non-toxic growth hormone can be produced in sufficient quantities to be effective in man, it may prove a valuable adjunct to routine measures in postoperative management.

MEDICAL ASPECTS OF THE KOREAN CAMPAIGN

THE United Nations Korean campaign has presented the medical services with plenty of difficulties and some new puzzles. Speaking in Melbourne in December, Dr. B. Gandevia,[7] of the Australian battalion of the Commonwealth brigade, quoted a description of Korea as "a fæcal country covered by dust in the summer and snow in the winter," where one may meet almost every disease in the textbooks. In such circumstances the lives of a body of men may easily depend on the efficiency of routine hygiene precautions; so the disposal of excreta and the treatment of drinking-water must be strictly supervised. The lack of proper medical supervision among the North Koreans and Chinese troops makes prisoners as dangerous as any "bacterial warfare" weapon, carrying numerous troublesome infections into the United Nations lines. It speaks well for the medical attention received at all stages by the Australians evacuated sick, that in the three months October–December, 1951, only one out of these men died—and of acute diabetes. Descriptions of the fierce cold of the Korean winter recall Hilaire Belloc's account of Napoleon's retreat from Moscow:

> "The sentries felt for the first time no longer discomfort, even of that acute and gnawing sort which seems to those who read of it under civilian conditions to be a hell; what they felt as the night advanced was a thing new to them, and perfectly intolerable to humankind—a thing no Westerner among them had yet known—the winter advancing from out of Asia, from the Frozen Steppes."

The cold of Korea, striking men who mostly come from warm climates, at first caused widespread frostbite; but there were few serious cases, and the troops soon learnt not to take liberties with temperatures below 0°F. In men over 35 and some others, especially those with old injuries of the spine and limbs, the cold caused disabling pains in the joints and muscles.

Among the diagnostic teasers encountered in Korea is the curious "acute epidemic hæmorrhagic fever" already noted in these columns.[8] This was listed in the U.S. Surgeon-General's reports as the cause of 25 deaths among 187 cases up to Oct. 22, 1951. Beard,[9] of the Australian Army Medical Corps, gives details of this disease, which has occurred in epidemics among the Japanese troops in Manchuria since 1935. It first appeared among U.N. forces in Korea early last summer; the incidence then gradually fell, to rise sharply again in October and November, when there were about 15 new cases a week. After 14–21 days' incubation and a short prodromal stage of malaise, anorexia, nausea, and limb pains, the temperature rises rapidly to 103°–105°F and more distinctive symptoms appear, the main ones being hiccup, sore eyes with blurred vision, oliguria, and manifestations of capillary hæmorrhages—petechiæ, especially on the face and upper trunk, bleeding from the gums and nose, melæna, and hæmaturia. Beard comments on the peculiar odour of the patient. The white-cell count rises to about 50,000 per c.mm. (mostly polymorphs) but the platelets are apparently diminished. Albumin, blood, and casts appear in a urine of specific gravity 1005–1010; the blood-urea rises, though not seriously. This acute stage lasts 3–5 days, when most patients improve, with diuresis and a return of appetite; but some get worse for a time even when they are afebrile, and they may become delirious and develop fresh hæmorrhages. In cases likely to be fatal, ominous signs are bradycardia, persistent hiccup, and hæmoptysis; cerebral hæmorrhage sometimes occurs and is nearly always fatal. Necropsy shows capillary disturbances and hæmorrhages in many organs; the kidneys are swollen, with glomeruli and proximal tubules full of blood; and the liver contains many degenerate cells. Japanese workers established the cause of the disease as a filterable virus probably spread by the mite *Lælaps jettmari* Vitzthum, a parasite of the field-mouse *Apodemus agrarius* which is found all over Korea. The infection is most prevalent in swampy ground near rivers where high grass grows, and it may well have come with the Chinese troops from Manchuria. In treatment, antibiotics have so far been unsuccessful, but benefit has been reported after transfusions of 200–500 ml. of blood collected from convalescent patients in the 2nd or 3rd week of illness, and a restricted fluid intake has been advocated. Otherwise, apart from barbiturates when sedation is needed and oxygen for respiratory distress, the only drugs given are vitamins C and K, which have not been strikingly successful.

Another odd disease is the kind of virus pneumonia reported by Troen.[10] This broke out explosively among evacuees from Korea and attacked 7 of the doctors and 5 of the nurses in the hospital where they were treated. There is high pyrexia; stiffness of the neck suggesting meningeal involvement; a maculopapular rash, sometimes hæmorrhagic; and occasionally enlargement of the liver and spleen. Radiography of the lungs reveals the patchy lesions seen in other virus pneumonias. All these patients recovered; mostly in a few days, though some took longer. Their sera contained no cold-agglutinins, which are usually present in primary atypical pneumonia, and did not respond to tests for psittacosis, Q fever, or influenza. Scrub typhus, one of the endemic diseases of Korea, seems a possible diagnosis, but the Weil-Felix reactions were negative. The ætiology therefore remains unknown. Antibiotics have been ineffective, and the treatment is purely symptomatic.

Korea is one of the places where the newly qualified medical man, called up for National Service, may be posted. He seems likely to find the country's endemic and epidemic diseases as astonishing as its geography and parasitology—not to mention its weather.

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[4] Taylor, F. M. L., Davidson, C. S., Levinson, S. M. *Conn. med. J.* 1944, 8, 141.

[5] Stevenson, J. A. F., Whittacker, J., Kark, R. M. *Brit. med. J.* 1946, ii, 45.

[6] Selye, H. *Endocrinology*, 1951, 49, 197.

[7] Gandevia, B. *Med. J. Aust.* 1952, i, 307.

[8] *Lancet*, 1951, ii, 1148.

[9] Beard, D. D. *Med. J. Aust.* 1952, i, 294.

[10] Troen, P. *Arch. intern. Med.* 1952, 89, 258.

Special Articles

MORTALITY FROM CORONARY AND MYOCARDIAL DISEASE IN DIFFERENT SOCIAL CLASSES

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THE occupational mortality analysis for the three years 1930–32 (Registrar General 1938) revealed striking differences between coronary disease and myocardial disease in relation to social class.

Allowing for differences in the age composition of the five social classes, deaths of males assigned to coronary disease, including angina pectoris, were highest in social class I (professional occupations) and lowest in social classes IV and V (unskilled workers). On the other hand, deaths classified to the group of myocardial diseases, including myocardial and cardiovascular degeneration, were lowest in social class I and highest in social class V (table I and fig. 1).

TABLE I—STANDARDISED MORTALITY RATIOS OF MALES AGED 35–64 BY SOCIAL CLASS IN ENGLAND AND WALES 1930–32

Social class	Coronary disease, angina pectoris	Myocardial disease, cardio-vascular disease
I Professional	237	77
II Intermediate between I and III ..	148	92
III Skilled workers	95	94
IV Intermediate between III and V ..	66	105
V Unskilled workers	67	122
All males aged 35–64	100	100

Among the various suggestions put forward to explain these contrasting mortality gradients are occupational and social class differences in dietary (Registrar General 1938), in mental stress (Ryle and Russell 1949, Stewart 1950), in physical activity (Stocks 1951, Rentoul 1951), and in death certification (Platt 1951).

INCREASING MORTALITY FROM CORONARY DISEASE

Whatever the true explanation for these social class differences it must be remembered that the evidence on which they were established is now twenty years old, and that during the past twenty years the incidence of coronary disease, judged from medical certificates of cause of death, has increased tremendously. Recent changes in methods of classifying the causes of death being taken into account, the death-rate (all ages) ascribed to coronary disease, including angina pectoris, increased for males from 216 per million in 1931 to 1339 per million in 1949; and for females from 87 per million in 1931 to 682 per million in 1949. Some of this increase can be explained by the increasing average age of the population; but, even when this is allowed for, mortality of males from coronary disease increased five times, and of females almost six times, between 1931 and 1949. Mortality ascribed to myocardial diseases, on the other hand, increased to some extent between 1931 and 1940, but has since then been declining (fig. 2). The recent trends of mortality from coronary disease and myocardial disease have been discussed in some detail by Ryle and Russell (1949), the Registrar General (1949, 1951) and Morris (1951); but it remains debatable how much the recorded increase in mortality from coronary disease is real, and how much can be explained by changing standards of diagnosis and fashions of certification. Here, as in many similar situations, the truth lies probably between the two sides, but how far to one side or the other remains to be determined.

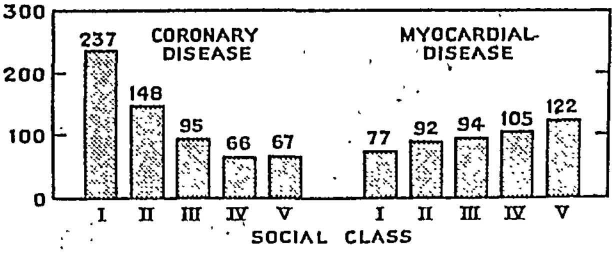

Fig. 1—Standardised mortality ratios of males aged 35-64 by social class from coronary disease (International List, 4th revision, no. 94) and from myocardial disease (International List, 4th revision, no. 93) in England and Wales in 1930-32.

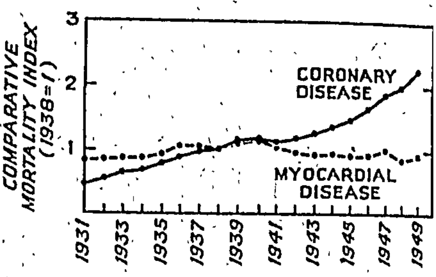

Fig. 2—Comparative mortality indices for coronary disease and for myocardial disease in males (all ages) in England and Wales in 1931-49. (For actual values see Registrar General's Statistical Reviews for 1942 and 1949, part I, Medical, table 8, nos. 93 and 94.)

SOCIAL CLASS DIFFERENCES IN 1949

As the importance of coronary disease as a certified cause of death has so greatly increased since 1930–32, the question naturally arises how far the social class gradient of mortality then evident still persists. As the recorded incidence of coronary disease has increased, has the incidence in each of the social classes increased by equal amounts, or have the differences widened or become less? For a proper answer to these questions the results must be awaited of the next Occupational Mortality analysis, which will be based on the occupational distribution of the population determined by the census of 1951 and the occupational distribution of mortality during the five years 1949–53. It will therefore be some years before these results are available, but in the meantime a rough indication of what may be expected can be obtained from preliminary scrutiny of the distribution of mortality by social class in 1949. Only a proportionate distribution can be given meanwhile, since the census details of the population are not yet known.

TABLE II—PERCENTAGE DISTRIBUTION OF DEATHS OF MALES AGED 45–74 BY SOCIAL CLASS IN ENGLAND AND WALES 1930–32 AND 1949

Social class	1930–32		1949	
	Coronary disease (4th revision, no. 94)[1]	Myocardial disease (4th revision, no. 93)[1]	Coronary disease (6th revision, no. 420)[1]	Myocardial disease (6th revision, no. 422)[1]
I Professional ..	8	3	6	3
II Intermediate between I and III	20	17	18	15
III Skilled workers ..	40	41	48	43
IV Intermediate between III and V	11	17	13	17
V Unskilled workers	10	20	14	20
Unoccupied or unstated	2	2	1	2
Total ..	100	100	100	100
Number of deaths ..	11,160[2]	46,041[2]	21,036[3]	13,002[3]

1. International Statistical Classification of Cause of Death.
2. In three years.
3. In one year.

Table II and fig. 3 show the percentage distribution by social class of deaths of males aged 45–74 assigned to the coronary group and the myocardial group of diseases in 1930–32 and 1949. Changes of statistical classification between the two periods have been ignored: these changes were considerable, but it is not possible to determine to what extent they affect the five social classes differentially.

In 1930–32, 37% of the deaths of males aged 45–74 from coronary disease were in social classes I and II, compared with 20% of deaths from myocardial disease. At the other end of the social scale 22% of coronary and 38% of myocardial deaths were in social classes IV and V. These differences are, of course, consistent with those already shown in table I.

In 1949, 24% of deaths assigned to coronary disease were in social classes I and II, compared with 18% of deaths from myocardial disease; and 27% of coronary and 37% of myocardial deaths were in social classes IV and V.

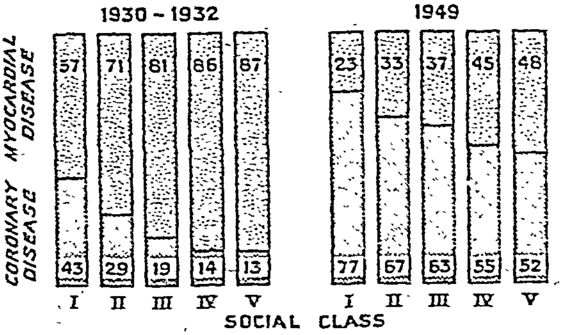

Fig. 3—Percentage proportions of deaths from coronary disease and from myocardial disease in males aged 45-74 by social class in England and Wales in 1930-32 and 1949.

Assuming that there has been no great transfer of population from one social class to another, and no very different age changes within the various social classes, it may be tentatively concluded:

(1) That the gradient of mortality from myocardial disease, increasing in 1930–32 from social class I to social class V, was still present in 1949.

(2) That the contrasting gradient of mortality from coronary disease, declining in 1930–32 from social class I to social class V, has become less evident in 1949.

The numbers of deaths of males aged 45–74 classified to coronary or to myocardial disease in 1930–32 and 1949 in each social class are directly compared in table III and fig. 3, where deaths from coronary disease are expressed as a percentage of the combined total of deaths from coronary and from myocardial disease. For all males aged 45–74 the proportion of coronary deaths increased from 20 to 61%. In 1930–32 the proportion of deaths from coronary disease in social class I (44%) was four times that in social class V (11%). The position had altered considerably by 1949, when the proportion of deaths from coronary disease in social class I (76%) was only 1·5 times that in social class V (52%).

TABLE III—DEATHS OF MALES AGED 45–74 FROM CORONARY DISEASE AND FROM MYOCARDIAL DISEASE; DEATHS FROM CORONARY DISEASE PER CENT OF COMBINED TOTAL OF CORONARY AND MYOCARDIAL DISEASE; BY SOCIAL CLASS IN ENGLAND AND WALES 1930–32 AND 1949

Social class	1930–32			1949		
	Coronary disease	Myocardial disease	Coronary % of total	Coronary disease	Myocardial disease	Coronary % of total
I Professional ..	935	1214	44	1184	367	76
II Intermediate between I and III	3142	7648	29	4252	2080	67
III Skilled workers..	4389	18,463	19	10,350	6119	63
IV Intermediate between III and V	1273	7877	14	2849	2316	55
V Unskilled workers	1164	9163	11	3064	2778	52
Total (including unoccupied)	11,160	45,041	20	21,935	13,902	61

TABLE IV—DEATHS OF MALES AGED 45–74 FROM CORONARY DISEASE AND FROM MYOCARDIAL DISEASE; DEATHS FROM CORONARY DISEASE PER CENT OF COMBINED TOTAL OF CORONARY AND MYOCARDIAL DISEASE; BY SUB-CLASSES OF SOCIAL CLASSES III, IV, AND V IN ENGLAND AND WALES 1949

Social sub-class	Coronary disease	Myocardial disease	Coronary disease % of total
IIIa Mineworkers (all types) ..	534	612	47
IIIb Transport workers	911	461	66
IIIc Clerical workers	1110	451	71
IIId Armed Forces	145	135	52
IIIe Others in social class III ..	7650	4460	63
IVa Agricultural workers	680	674	50
IVb Others in social class IV ..	2169	1642	57
Va Building and dock labourers..	486	498	49
Vb Others in social class V ..	2578	2280	53

In addition to distinguishing the five principal social classes the occupational analysis for 1949–53 will also differentiate between five sub-classes of social class III and two sub-classes of social classes IV and V. The occupational composition of these sub-classes, and the deaths from coronary disease per cent of deaths from coronary and myocardial disease in each sub-class in 1949, are given in table IV. In social class III the proportion of deaths from coronary disease was highest among clerical workers (71%) and lowest among mineworkers (47%), a finding consistent with the suggestions of Stocks (1951) and Rentoul (1951) that sedentary occupation predisposes to the coronary rather than the myocardial type of cardiac disease.

SUMMARY

The Occupational Mortality analysis of 1930–32 showed that mortality attributed to coronary disease was highest in social class I (professional occupations) and lowest in social classes IV and V (unskilled workers). Mortality from myocardial disease showed the reverse tendency.

The recorded mortality from coronary disease in 1949 was five times higher for males and six times higher for females than in 1931.

The proportionate distribution of deaths by social class in 1949 suggests that the social class differences of mortality for myocardial disease have not changed, but that those of coronary disease have become less.

The ratios of deaths from coronary disease to the total of deaths from coronary and myocardial disease increased less in social class I than in social class V between 1930–32 and 1949. The ratio in 1949 was high among clerical workers and low among mineworkers.

REFERENCES

Morris, J. N. (1951) *Lancet*, i, 1, 69.
Platt, R. (1951) *Ibid*, p. 51.
Registrar General for England and Wales (1938) Decennial Supplement 1931, Part IIA, Occupational Mortality. London.
— (1949) Statistical Review of England and Wales 1940–45, Text Vol. I. Medical. London.
— (1951) Statistical Review of England and Wales 1946–47, Text Vol. I. Medical. London.
Rentoul, E. (1951) *Lancet*, i, 587.
Ryle, J. A., Russell, W. T. (1949) *Brit. Heart J.* ii, 370.
Stewart, I. McD. G. (1950) *Lancet*, ii, 876.
Stocks, P. (1951) *Ibid*, i, 351.

Before our Time

BROWN-SÉQUARD

A Biographical Essay

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On April 1, 1894, Charles Édouard Brown-Séquard died in Paris, and with his passing the great French school of experimental physiology which had known no equal came to an end. To it had also belonged Magendie, Flourens, and the level-headed Claude Bernard, whose dictum it was that the scientist must shed prejudice with his overcoat before going into the laboratory. It is disconcerting to realise the achievement of these men, for they found physiological knowledge at the beginning of the 19th century much as Galen left it in A.D. 200, and yet left it recognisably as it is today.

EARLY YEARS IN PARIS

Brown-Séquard [1] was born on April 8, 1817, at Port Louis in Mauritius, the son of a French mother and an Irish-American father but by accident of birth (since the island had been captured from the French in 1810) a British subject. Little is known of his childhood and schooldays, but at the age of 19 he set out for France, accompanied by his mother, to seek fame in the Parisian literary world. Though dreams of making a name as a writer long followed him, he soon destroyed the manuscripts he had brought from oversea and enrolled as a medical student, applying himself with the most rigorous discipline to his task.

By 1842 he was clerking as externe for Trousseau, the ablest clinician of the day, and had already had some experience of animal experiment in one of the small private laboratories, which then flourished in Paris. Having obtained a coveted post as a hospital interne, he suffered a heavy blow in his mother's sudden death, which so upset him that he left France abruptly for Mauritius. Arriving there in the spring of 1843, he at once realised that he had made a mistake, the island was too small to contain his ambition; but it was some months before he could raise the price of his return passage. He qualified in 1846, taking his doctor's degree with a thesis relating some observations on reflex activity and transmission of sensation in the spinal cord, work which was an earnest of things to come.

For the next five years, despite desperate poverty, he devoted himself largely to physiological experiment, which he did in his lodgings, where he also housed his animals. Unwillingly—but to pay for this work—he also engaged in some kind of medical practice, the details of which are obscure, though it is known that he served in a Paris military hospital in 1849 during an outbreak of cholera. He was a regular contributor at meetings of the Société de Biologie from its foundation in 1848, and one of its earliest secretaries. Writing long afterwards of the years between 1843 and 1851, he remarked that he had worked

> "very hard, taking no exercise, and living in a vitiated atmosphere. I slept very little, and usually passed eighteen or nineteen hours a day writing, reading or experimenting. My diet was miserable, and with the object of avoiding the need of much food, I took a great deal of coffee. I gradually, though slowly became exceedingly weak."

FIRST CONTACTS WITH AMERICA

At the beginning of 1852, seeing no future for himself in Paris except a perpetuation of this kind of life, he made up his mind to go to America. He set sail with scarcely a word of English, and landed in June in Philadelphia, bringing a letter from Broca addressed to the University of Pennsylvania, which ran:

> "For eight years Brown-Séquard has exhausted his resources and imposed upon himself incredible sacrifices in order to carry out expensive researches in experimental physiology. Today he has nothing left save an honourable character, profound erudition, and scientific articles which everyone can appreciate."

With this introduction, he spent a year giving lectures on the pathways of sensation in the spinal cord, on the function of the cervical sympathetic nerve, and other topics, in Philadelphia, Boston, and New York. But his sojourn did not bring him a settled post in an established medical school. He had to eke out the earnings of his lectureships, teaching French and delivering babies at cut-rate prices, and after a year he longed for Paris once more. When he sailed in July, 1853, he carried with him both a newly married American wife and public regret at his going

> "not only on account of the many original views which he has presented to us as the result of his own observations . . . but on account of his attractive qualities as an amiable and honorable man."

Prospects in Paris, however, soon proved unhopeful as ever, and his thoughts turned once more, and for the last time, to the possibility of life in Mauritius. In the middle of May, 1854, Brown-Séquard and his wife arrived at Port Louis, to find that an epidemic of cholera, in which 8000 people died, had just got under way. He immediately helped organise a hospital and, with another physician, treated the sick. He prescribed opium for his patients, at that date a new idea but one which became staple medical practice until the advent of Sir Leonard Rogers's fluid-and-electrolyte replacement therapy. According to legend Brown-Séquard, one day imagining the symptoms of cholera upon himself, took so large a dose of laudanum that he nearly died.

When the epidemic was over, he became restless to leave the island. For once fortune favoured him, for he unexpectedly received the offer of a professorial chair at the Medical College of Virginia which he accepted.

He arrived in Richmond some time in the late autumn of 1854, where it promptly turned out that everything was not, after all, going to be blissful. His colleagues of the faculty discovered a dislike of what they called his "surplus of honesty," and by some perversion of the truth labelled him lacking in energy. A witness afterwards recalled of his lectures that his "discourse was not very unlike an attack of spasmodic asthma, and frequently his agony in trying to make himself comprehended was, if anything, greater than ours in trying to comprehend him," while his practical demonstrations were looked on "with pleased astonishment, like wonders wrought by a stage magician"—observations which suggest that the general atmosphere was a hostile one. Brown-Séquard resigned at the end of a term.

RECOGNITION

Back in Paris, still without any public appointment, he now built up a considerable clinical practice, which allowed him to spend time and money on private experiment. In 1858 he came to England to lecture on his researches before the Royal College of Surgeons,[2] and for the next few years, until 1863, he made his home in London. During this period he received many honours. In 1860 he was elected to the fellowship of the Royal Society, of the Royal College of Physicians, and of the Royal Faculty of Physicians and Surgeons of Glasgow. In the same year he was also appointed as physician to he newly founded National Hospital for the Paralysed nd Epileptic, Queen Square, London, an appointment hich did honour as much to the hospital as to the man. he young Hughlings Jackson, who had come from ork in 1859, fell under his influence. According to ir Jonathan Hutchinson, his lifelong friend, Jackson as strongly advised that if he wished to attain anything e should not diffuse his effort, but must keep to the ervous system—most palatable advice, for it came close Jackson's own wish.

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[1] His birth certificate bore the name Charles Édouard Brown. He did not take his mother's patronymic till 1846, and only legally regularised its use twelve years later.

[2] These lectures were first published in THE LANCET in 1858, and in 1860 in book form as *The Physiology and Pathology of the Central Nervous System.*

In London Brown-Séquard had quickly gathered a crative consulting practice. But for success of this kind e never cared, except in so far as it allowed him to chieve his objects as a physiologist. It was said by an bituarist that he had once refused to go to Italy to see n American boy, because he believed he was not the right erson to advise upon the case, though he was offered a ift of £10,000. On another occasion, while in London, e was asked to visit a patient in Liverpool for a fee of 200. He replied that he would shortly be in that city n route for America and would willingly see the case at is ordinary fee.

In 1864 he once more set off for America, this time as rofessor of the physiology and diseases of the nervous stem at Harvard Medical School, where he remained—lbeit intermittently—until the beginning of 1868. ossibly the death of his wife shortly before, which left im with a 12-year-old son, had something to do with is decision to return to France. Although in 1869 he as for the first time given an official appointment, in xperimental and comparative pathology, at the École e Médecine, it was not of professorial rank, apparently mply because he was still not a French citizen; and 870 found him again in America. For the next eight years, y his own account the unhappiest of his life, he was an nquiet traveller, living mostly in New York with frequent xcursions to Europe. In 1872 he married for the second ime an American wife, but she did not long survive the irth of a daughter in 1874, and in 1877 he was married r a third time to an Englishwoman, the widow of a ainter.

On Feb. 10, 1878, Claude Bernard died, and at last here was the chance of an appointment worthy of rown-Séquard's talents and fame in the only city here he really cared to be. In May, as a preliminary, e took out naturalisation papers, and at last became in ct what he had always been in spirit, a true Frenchman. n August he was duly appointed Bernard's successor as rofessor of medicine in the Collège de France, an office hich he happily fulfilled till his death fifteen years later.

HIS CONTRIBUTION

Without doubt Brown-Séquard was a giant among en. Gifted with a ceaselessly inquiring and intuitive nind, his thought so rapid that it seemed, a contemporary oted, to savour of revelation. He disciplined himself to single and undeviating purpose of life—"to know omething more than the general run of men," a phrase rom one of his earliest letters. If for much of his own lifeime he seemed to be overshadowed by Claude Bernard, his was at least in part fortuitous, because, as Broca nce said, "he is not a Frenchman, although educated t Paris and speaking the language like one of us: lthough acknowledged to be possessed of eminent talent, e has nevertheless been unable to attain any official position, only because he is a foreigner." Looking back now, he may even strike one as the more brilliant of the two, though certainly the more fitful and wayward.

If one reads his essays on the physiology of the spinal cord—they are well worth study by the specialist—and follows the steps by which he deduced the pathways of sensation therein, it is impossible not to be impressed by the care and patience of his work, checked and rechecked as it was time after time in many animals, always adding a little more. One must wonder too at the minute accuracy of his observation, and at the tremendous technical skill which he must have brought to his operations. He insisted repeatedly on the principle of action at a distance within the nervous system—i.e., that neural activity at one point is always coloured and conditioned by what is happening at another and remote point—and though some of his instances have proved wrong, the conception is one which later was independently elaborated by Sherrington and its full implications are still to be explored. He was the first to appreciate the autonomic nervous control of blood-vessels and of the secretion of glands, and to recognise that alterations in body-temperature reflect changes in vascular tone. He proposed the idea that in activity a tissue demands a greater blood-flow than when it is at rest, and he always had the liveliest interest in problems of tissue circulation.

After Addison published his observations in 1855 on the clinical effect of disease of the suprarenal capsules, Brown-Séquard established that the ablation of these glands in animals speedily led to death, and he gave a full account of the symptoms of adrenalectomy. From various experiments he perceived that these organs must be making some important secretions into the blood, the absence of which was fatal. This led him later to the speculation that perhaps all glands, even those having an obvious external secretion, such as the testicle and the pancreas, might elaborate substances for release into the blood-stream, which were important for bodily economy. As early as 1875 he was experimenting with testicular grafts in animals as a means of counteracting senescence, and the last few years of his life were spent seeking to isolate a testicular hormone, a pursuit which made him a laughing-stock with his scientific colleagues. But he was wiser than they knew.

Personal Papers

PAROXYSMAL AURICULAR FIBRILLATION

A FEW days of unexpected leisure and the encouragement of a colleague has led me to write these notes of medical autobiography in the hope that they may prove of value or interest to others in like case; for paroxysmal auricular fibrillation in an otherwise normal heart is a rare condition and its ætiology is unknown.

Despite a weight well below the average normal, a nervous constitution, and a temperament far from placid, I negotiated childhood and adolescence, public-school and university education, a London hospital and the usual residential appointments, World War I, and early years in consulting practice, without untoward event in the chronicle of health. However, a love of good food and a surfeit of crêpes suzettes at a well-known restaurant on the Continent led in 1936, at the age of 39, to a first attack of auricular fibrillation lasting a few hours and disappearing spontaneously. The attack was repeated three to four months later and as readily disappeared.

Counsel's opinion was sought, and paroxysmal auricular fibrillation confirmed in a heart otherwise normal in all respects. Intervals between the attacks gradually decreased, as had been foretold, and by 1938 they were occurring about twice a week. Various investigations of alimentary function were undertaken; a battery of biochemical blood-estimations was carried out; and, as a final act of propitiation or expiation, the tonsils were sacrificed. The attacks continued, and quinidine was tried in dosage of gr. 3 t.d.s. as a preventive and four-hourly during attacks. Prevention seemed effective at first and would postpone an attack for twenty-four hours, but no longer. The attacks themselves gradually became longer, requiring larger doses for the restitution of normal rhythm. Usually they would start after lunch and last until the early hours of the following morning. At times the quinidine produced unpleasant gastro-intestinal symptoms such as nausea, slight epigastric pain, and diarrhœa. The last-named was occasionally followed by a vasovagal attack, with, on one occasion, temporary loss of consciousness. These attacks were wont to appear during the periods of reversion to normal rhythm.

The rate of the heart in fibrillation and at rest was 90 per minute, and during the episodes the only tolerable exertion was walking on the flat, which could be undertaken in reasonable comfort. During the attack, too, there was a general feeling of unease in the precordium, obvious limitation in one's capacity all round (mental and physical), and particularly a sense of heaviness in the legs after exertion. In fact the dominant effect during the attacks was one of fatigue. Dyspnœa was very rarely experienced. During the periods of normal rhythm any form of exercise could be indulged in without apparent ill effect. The chief precipitating factor of the attacks was the taking of food, and especially of large meals: these were by far the commonest antecedent factors; others of less note were exercise and emotional episodes. At times it even seemed that a change of mood from gay to grave would hold up an attack. At no time was there any indigestion, and minor attacks of colon neurosis bore no relation to the fibrillation. Exercise had a curious and variable effect. If an attack was imminent, and one could sense its approach either by a series of extra-systoles or a vague unease, not pain, in the precordium, one could often play a round of golf with the certainty that as soon as it was over the fibrillation would start. On another occasion, while walking up Snowdon by the Pyg track slowly during a paroxysm, the heart resumed normal rhythm during a momentary pause.

At this period of the illness it was the greatest relief to get into normal rhythm, though the effect of the quinidine was always disagreeable. Finally at the end of the late war the attacks were occurring about twice in twenty-four hours, and the daily dose of quinidine had risen to gr. 45 in order to prevent their increase. It was clearly a losing battle, and learned counsel's opinion was again sought. This contained strong advice to stop the quinidine altogether, let the auricle fibrillate, and control the ventricle with digitalis, which had so far not been used. This advice was followed. After discontinuing the quinidine there was one further paroxysm which disappeared spontaneously, and then, after a few days' interval, the establishment of permanent fibrillation, which to date has meant five years.

The effects of this change were remarkable. It has resulted in a great improvement in general health, and as a rule complete unconsciousness of the heart's action, even when playing a round of golf and pulling a caddie cart. Digitalis folia, gr. 1½ daily, keeps the ventricular rate between 60 and 70 at rest. Walking can be undertaken in comfort provided the gradient is not too steep, while trout-fishing is an ideal recreation. The only cause of consciousness of the heart's action, apart from excessive exertion, is a big meal, especially if taken with alcohol and in a hot room. This is wont to produce some increase in rate and a sense of discomfort; a small price, perhaps, to pay for one of the few pleasures that are left to us.

"... There is a tombstone in a little Scotch burying ground which reads, '*Here lies the body of Tammas Jones*, who was born a man and died a grocer.' That tragi-comedy is being enacted in countless permutations and combinations in our modern world. A recent writer in my own field says that this depersonalization of human life is the major tragedy of our time.... In medicine the pressures are so great upon a man's time and strength that he runs the risk, unless he fights against it consciously, of writing his own epitaph in advance, 'Here lies the body of Hiram Smythe, who was born a man and died a gastroenterologist.'"—WILLARD L. SPERRY, *Ethical Basis of Medical Practice*, London, 1952.

In England Now

A Running Commentary by Peripatetic Correspondents

THANK heaven for a proper sense of values! I arranged to attend a weekend conference on medical teaching, forgetting that it coincided with the date of the Boat Race. Rather than skip the conference altogether I had planned to leave the afternoon meeting surreptitiously and listen to the race on my car radio. However, this was quite unnecessary. The chairman wisely decided that the session should be interrupted for an "important athletic event," and at 3.15 P.M. the commentary on a portable wireless drowned the speaker. Levity took the place of learning; some money changed hands; and the meeting went on as before.

* * *

Some weeks ago I appealed unsuccessfully in these columns for a good working Witch. My maid's warts eventually disappeared under N.H.S. specialist treatment; but now I need the services of a competent Exorcist. The Bastard Boys, two early 19th-century lead cupids with baskets on their heads—hence the etymological confusion—which were bought to fill two niches recently unbricked in our Elizabethan garden wall, seem to have brought a curse with them. Coming back from the establishment at Isleworth where they were acquired, my car ran out of petrol and had to be towed home because the anti-thief cap on the tank resisted all efforts to open it. Next morning the maid's room was found to be briskly on fire, and, although it was put out before the fire brigade arrived, a restful Sunday morning was not had by all. Then a succession of sore throats, lumbago, and dental troubles descended on a normally healthy household, and the cat disappeared for 24 hours after overturning some just-sown seed-boxes. Now the "load of good, earthy loam" on the bed beneath the B.B.s has turned into gravel, clay, and couch-grass.

The formidable list of medical auxiliaries in the N.H.S. fails to include Exorcists—a serious gap—and I shall have to go outside the service. But diagnosis should precede treatment, and perhaps the next step is to borrow some holy water from the church whose doors I pass daily and apply it to the B.B.s in the Anathema Patch Test (Mephistopheles et al.). I think it will fizz.

* * *

Lin, aged five, to her dilatory mother: "Mummy, I should have this baby now and be done with it."

* * *

My own peripatetics are members of the *Helix* family (or maybe the helicidæ all keep to the land); anyway, these are water-snails of three or four different sorts which live in a largish tank on my library table. Not long since, I was smitten with curiosity about how and why the water-snail goes from place to place. Herewith the results of my profound researches.

The snail, whether white or red, pointed or curled, is a beast of small discernment. When a piece of meat was suspended in the tank on a cotton thread the snails did not discover it for 24 hours, though when it was dropped on the bottom of the tank [illegible] half an hour. It may be argued [illegible] snail would travel up and down a [illegible] the chance of finding somethi[illegible] end. Well, two of them did; the[illegible] and a very small red, hatched a month or so ago, which had attached itself to the white's back. The white devoured the meat, but the little red Old Man of the Sea, in spite of its close proximity, paid no attention to the meat whatever. The patriarchs, well versed on the limits and potentialities of the aquarium also refused to be drawn by the free meat ration—perhaps the thread was more than they could manage. Not that climbing up the thread was their only way to reach the meat. A snail can walk on the surface of water—to be exact, he spreads out his foot just below the surface to make surface tension hold him up, and then crawls along upside down; he travels quite fast like this. He can also swim freely though very slowly, right side up. Even more common (and more puzzling) is the snail's ability to fall suddenly to the bottom of the tank and, equally suddenly, to rise to the top. When he wants to fall he expels some air, but how he gets up again I don't know. That he does these things is beyond all doubt—I have seen it all dozens of times. One other point I hoped to settle was whether snails answer to their names. I could reach no definite decision on this for it seems doubtful whether snails have any names. Nor are they good mothers—the last clutch of eggs laid in the tank was at once eaten and the mother (a red one) is under grave suspicion. But they do love giving each other rides.

* * *

The Braes of Tummel,
N.B.

Dear Professor Burnham-Woode,

re McBeth, Lady F.
Dunsinane Castle, alleged of Inverness

I am grateful for your report of March 22 on my patient but trust your diagnosis is more accurate than your geography. Birnam is more than 20 miles from the nearest point in Inverness. Like a worthy Scot I believe in ancestor-worship, but that even my forbears carried trees that distance is a story too tall for even a Highlander to swallow.

For me, the Shakespeare-Bacon controversy is finally settled by your letter. If a Baconian professor has made this egregious mistake he clearly cannot have inherited any of the great William's genes.

Yours critically,
ALEXANDER ALASTAIR HAMISH MCPHAIL.

* * *

Not being in general practice I don't see much of medicine in the home, but I get a curious glimpse of it from our parish magazine's monthly tips on "nursing." The diagnoses and remedies described by the housewife-contributors reveal a strange blend of pseudo-science and medievalism. Thus:

> "*To visitors.*—Never enter a sick-room in a state of perspiration (to remain any time), for when the body becomes cold it is in a state likely to absorb the infection. Never with an empty stomach visit a sick person (if the complaint be of a contagious nature). In attending a sick person do not stand between the patient and any fire which may be in the room, as the heat draws the infectious vapour in your direction."

Sometimes the doctor seems to be in for a difficult interview—for example, we learn that "Many cases of pain previously classed as lumbago, neuritis, &c., are really due to spinal trouble. I have found by experience that long-standing faulty posture is generally the cause. The doctor will tell you to practise correct sitting and standing positions whenever possible, so that they may become second nature. Avoid slumping in your easy chair and crouching over the table when writing." I remember being taught to sit up in the nursery, but the subject was left out of my clinical training. There are often hints of desperate personal problems:

> "*Falling hair.*—Sometimes one discovers a bald patch on one's head. This, if not attended to, increases. Here is a remedy. Buy from your chemist 2 or 3 oz. of oil of nutmeg. Rub this in the hairless patches 2 or 3 times daily. In a very little time you will see the hair is growing. Tried by a Hospital Sister when all else had failed, and strongly recommended."

Poor sister! One can imagine her adjusting her cap to hide the patch from the housemen; then at last the nutmeg saves her.

Hiccups are famous for nostrums. Didn't the *Times* say that one sufferer received 900 suggestions in answer to an advertisement? I wonder if they included these:

> "Get someone to hold your right-hand little finger about half-way. This sounds simple, but it works"; and "If you find an attack coming on press the tip of your tongue against the roof of your mouth and the hiccups will stop at once. The same remedy for those who have plates."

Some of my friends with plates might well try this without waiting for hiccups.

* * *

Children do not always interpret their first glimpse of breast-feeding as correctly as the little girl in THE LANCET of March 22 (p. 667). One small boy who saw a puppy having its feed ran to me with an expression of horror, crying: "Do you know what that puppy did? He *bit* his mother!"

Letters to the Editor

CEREBRAL SYMPTOMS IN CARDIAC INFARCTION

SIR,—Your annotation of March 29 prompts me to record the following case.

A man, aged 66 years, was admitted to hospital on Dec. 14, 1951, *as the result of sudden collapse at midday. From* his previous notes it was learnt that a duodenal ulcer had been diagnosed in 1940 and that he had suffered with chronic bronchitis for many years. In 1948 he had been admitted to hospital with a left-sided hemiplegia, from which he had made a satisfactory, but not complete, recovery. His blood-pressure was then 190/100 mm. Hg, and essential hypertension with a right cerebral thrombosis had been diagnosed.

At the time of his second admission he was collapsed, cyanosed, and cold, and was sweating profusely. The pulse was impalpable, the blood-pressure could not be recorded, and the heart-sounds were faint. The patient was conscious and able to comply with simple instructions, such as protruding the tongue; but he could not speak. Examination revealed weakness of the right lower facial muscles and the right arm and leg, which were spastic with increased tendon-reflexes. The right plantar response was extensor and the left flexor. A left cerebral hæmorrhage was diagnosed, and the patient was treated on expectant lines.

On the following day the patient's condition improved and he was able to recall that, at the time of his collapse, he had experienced a severe pain over the upper precordium which had radiated through to the back, and that he had felt numb and weak down the right side of the body. The signs of a left-sided cerebral lesion appeared unequivocal. There was pronounced weakness of the right lower face and flaccid weakness of the right arm and leg. Both plantar responses were now extensor. It was thought that the left extensor response might be due to extension of the hæmorrhage, or that the initial left flexor response might have been a false one and he had a left extensor response as a residuum of his earlier cerebral thrombosis. The blood-pressure was *170/105 mm. Hg; his urine contained a trace of albumin*; the erythrocyte-sedimentation rate (Westergren) was 45 mm. in the first hour; and his white blood-cell count was 18,300 per c.mm. with 86% polymorphs.

After his initial improvement the patient relapsed into coma and died on the fifth day after admission.

Necropsy revealed a recent infarct of the posterior wall of the left ventricle. The brain showed a zone of old cerebral softening in the right cerebral hemisphere, but the remainder of the brain appeared to be normal. The cerebral vessels were within normal limits, and there was no evidence of embolus.

From the physical examination of this patient there seemed to be little doubt of the diagnosis of left-sided cerebral vascular catastrophe, which was thought to be a hæmorrhage. This diagnosis was supported by the previous history that he was a known hypertensive and had been in hospital with a hemiplegia on the opposite side. The absence of a left-sided cerebral lesion at necropsy, and the finding of a posterior cardiac infarct, were therefore unexpected.

In retrospect it was interesting to correlate the finding of a posterior cardiac infarct with the patient's account of precordial pain, radiating to the back and associated with vomiting, which he had experienced at the same time as the right-sided weakness. The patient's history was not a clear one, and this account of precordial pain had been somewhat discounted in the presence of the obvious signs of hemiplegia. It would appear, however, that his symptoms of coronary infarction occurred at the same time as he first noted the right-sided weakness. The true diagnosis was revealed by necropsy and thereby resembles those few cases, mentioned in your annotation, where a cardiac infarction has manifested itself by hemiplegia. This case throws no further light on the mechanism of such neurological disturbances, and the selective interference with cerebral function remains an enigma.

This patient was admitted under the care of Dr. A. H. Douthwaite, to whom I am indebted for permission to publish the case-record.

Guy's Hospital, London, S.E.1. A. BATTY SHAW.

SPLENECTOMY

SIR,—It is evident from the articles by Sir Lionel Whitby and Mr. Maingot, in your issue of March 29, that primary acquired hæmolytic anæmia presents a problem both in diagnosis and in treatment.

Published reports, which I have reviewed,[1] seem to point to the following conclusions:

1. Splenic enlargement is by no means a constant feature of the disease.
2. Auto-agglutinins, sometimes active at room and body temperature, are a common source of difficulty and error in blood-grouping.
3. In the differentiation of acquired and congenital hæmolytic anæmia the Coombs test is of limited value.
4. To those exhibiting hæmoglobinuria a good prognosis may be extended.
5. The survival-rate in 54 patients receiving medical treatment alone was 81%; while of 40 who underwent *splenectomy* 70% recovered.

It may therefore be concluded that operative treatment is of value for those patients in whom continued transfusion is no longer practicable.

J. G. MILLICHAP
Senior Registrar,
Children's Department.

St. Bartholomew's Hospital,
London, E.C.1.

THE COST OF MEDICAL CARE

SIR,—Professor Titmuss (March 22) seems to fall into the error common to writers about America: he forgets that it is a vast continent of separate States, and that what is applicable to one part of that continent is by no means necessarily applicable to another.

Thus, in applying to the whole of the U.S.A. the inference drawn from the Californian study that "voluntary health insurance has been tried and found wanting," he does an injustice to the Health Insurance Plan of Greater New York. This is a pre-payment plan started in 1947 under which more than a quarter of a million people are receiving preventive, diagnostic, and curative medical services without any financial or other deterrent. The service is provided in the patient's own home, at doctors' surgeries, at hospitals, and at medical group centres.

Professor Titmuss says that "one reason for this partial failure of pre-payment plans is that they have to a large extent been limited to illness in hospital. It is medical care in the home, not in the hospital, that lands the American family in most expenditure. . . ."

Under the New York H.I.P. 85% of the doctors' services to subscribers are provided outside hospital. A prominent feature of the service is the organisation of medical group-practice at 30 centres distributed throughout New York City. These centres are as good as the best dream of those who would like the provision of such centres under our own National Health Service. Here general practitioners and specialists work side by side in warm, well-furnished, and well-equipped premises with clerk-receptionists, medical social workers, laboratory technicians serving clinical laboratories, radiographers serving X-ray plants, and nurses all at their elbows. If a general practitioner wants to consult a consultant about his case he *may* well be able to do so on the spot and save all the complications of referal to hospital, which may be so vexing a feature in this country both for patient and doctor. If this *on-the-spot consultation* reveals the need for an emergency operation an ambulance can be brought at once to remove the patient to hospital, where he may be followed up and operated upon by *the same surgeon* who saw him at the group-practice centre.

The cost to subscribers, in our money, works out at weekly rates of 7*s.* 2*d.* for a single person, 14*s.* 6*d.* for husband and wife, and 20*s.* 10*d.* for the whole family. The employer pays at least half of these costs in almost all cases, and in some instances he may pay all. Unlike our own National Health Service the scheme is completely solvent within itself, and makes no extraneous demands on taxpayers or ratepayers.

On the other hand, the scheme does not provide drugs, spectacles, and other appliances, dental care, psychotherapy, a child-guidance service, rehabilitation, home helps, medical services for patients confined to institutions for chronically ill.

Another injustice done by Professor Titmuss in survey of American arrangements for medical care his failure to mention the Veterans Administration whi for a population of approximately 20 million veter in the U.S.A., provides free a wide range of servi including general, medical, surgical, nursing, and den care, medicines, physiotherapy, corrective rehabilitati prosthetic appliances, mental hygiene, and other servi in hospitals and outpatient clinics, and through do ciliary visitation.

J. GREENWOOD WILSON.

Public Health Department,
City Hall, Cardiff.

MASS RADIOGRAPHY

SIR,—I have read with interest the letter from Nash (March 29).

Surely his remarks that the resources of the ma radiography units only enable some 10% of the popu tion to be X-rayed (and a selected 10% at that) supp the argument put forward by Dr. Grenville-Math and Dr. Trenchard (Feb. 9).

He remarks that in a chest-clinic area of 200,0 population the general practitioners would require 10 films a month, and that he does not know a chest cli that could manage this number. At this clinic (where 'Odelca' camera is in use) in the month of March, 19 634 people were X-rayed for the first time; and, witho altering the existing equipment or interfering with existing time-table, there would be no great difficulty increasing this number to 1000 should this clinic be only source of chest radiographs for the general prac tioners of the area.

I would add that this clinic serves a population 230,000, and that the 634 "new radiographs" taken March were over and above the large number of routi radiographic examinations carried out.

A. W. ANDERSON.

Chest Clinic,
Harrow, Middlesex.

β-NAPHTHYL-DI-2-CHLOROETHYLAMINE IN MULTIPLE MELANOMATOSIS

SIR,—In 1948 Haddow et al.[1] prepared a series aromatic nitrogen mustards. One of these produc —β-naphthyl-di-2-chloroethylamine (R48)—which administered orally, has been tested clinically, mainl in reticuloses and leukæmias. The results have bee inferior to those obtained with the β-chloro-alkylamin intravenously. No response was obtained in a patie with lymphosarcoma and in a patient with giant-ce follicular reticulosis.[2]

R48 has been used in the treatment of multip melanomatosis.[3] We have studied three cases of th condition while R48 was being administered. Trace experiments with P^{32} revealed a high uptake of the iso tope in two of these cases. In both these cases th uptake was greater after R48 had been administere and this corresponded with the clinical observatio that the melanomata had enlarged and become mor superficial.

CASE 1.—A man, aged 37, developed multiple melanoma tosis six months after laparotomy for abdominal melanoma tosis. Four months later (Dec. 13, 1950) the melanomat had grown considerably when treatment with R48, 100 mg thrice daily, was initiated. On Jan. 6, 1951, the patient developed *influenzal bronchopneumonia* which responde favourably to penicillin. Distressing nausea, occasional vomiting, and an absolute lymphopenia necessitated dis continuing the R48 on Jan. 11, when 8·7 g. had been given Subsequently the melanomata grew rapidly, and the patient died on Jan. 29.

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[1] *Arch Dis. Childh.* (In the press).

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1. Haddow, A., Kon, G. A. R., Ross, W. C. J. *Nature, Lond.* 1948, 162, 824.
2. Gardikas, G., Wilkinson, J. F. *Lancet*, 1951, i, 137.
3. Cade, S. Chemotherapy of Cancer. Liverpool, 1951.

dizzy and nauseated, and later vomited. When I saw him an hour later he was unable to sit in a chair without distress, and was most comfortable lying prone with his head turned to the right; he complained of tinnitus and mild left temporal headache. He stated that he had had a head cold for ten days, but that it was almost gone. He had nystagmus on deviation of the eyes to left, right, and upwards, most marked on looking to the left. His hearing was normal. The pharynx was mildly inflamed and the left eustachian tube was obstructed; the tympanic membranes appeared normal except that the left did not move. Twenty-four hours' treatment with chloramphenicol (1 g. 8-hourly), 'Dramamine' (100 mg. 8-hourly), and 'Neosynephrine' nose-drops rendered him free of symptoms, though nystagmus persisted for another twenty-four hours.

I have seen a patient with similar symptoms, but in addition severe headache and mild bilateral catarrhal otitis media, whose symptoms responded rather more slowly to the same medication. Two of my patients, on the other hand, had no evidence of upper respiratory infection or eustachian obstruction; their symptoms responded to dramamine in two or three days.

The syndrome of acute labyrinthine irritation may certainly be caused by eustachian obstruction as well as by middle-ear disease and affections of the labyrinth itself and its central connections; any of these may be involved in the course of various upper respiratory infections, so that it is perhaps unnecessary to postulate a specific disease-entity to account for the cases recently described.

I would stress the efficacy of dramamine in relieving the distressing and disabling symptoms associated with this syndrome.

U.S. Army Hospital,
Fort Benning,
Georgia, U.S.A.

D. E. MARMION.

BOVINE TUBERCULOSIS PREVENTS HUMAN TUBERCULOSIS?

SIR,—In his letter of March 15, Dr. McKinstry, medical officer of health for Jersey, states that my letter of Jan. 26 gives a wrong impression of the facts in Jersey. I will give figures to demonstrate that tuberculosis on the island is increasing as the cattle attestation scheme progresses:

Years	*No. of tuberculous patients admitted to hospital*
1925–29	49
1935–39	210
1945–49	313

This is the position after 10 years' complete attestation of the cattle on the island. Furthermore the death-rate is as high as in England and Wales, which has only about 20% of cattle attested.

My case is that ever since the initiation of the intradermal tuberculin test for cattle it has been assumed that the eradication of tuberculosis from cattle would lead to a reduction of this disease in mankind, but the facts reveal a precisely opposite result. The fall in the death-rate during the last few years is the result of improved treatment after infection has taken place. To prevent infection is superior to any treatment.

Dr. McKinstry remarks that tuberculosis did not exist to an appreciable extent in the cattle on the island. This may be true; but since the eradication of whatever tuberculosis did exist in cattle, human infection has increased seven times. It should be noted that the attested cattle scheme commenced in 1936. The fact is that increased human infection coincides with, and in my opinion is the result of, eradication of the infection in cattle.

In my earlier letter[1] I suggested that a substance (which I have called tuberculin) exists in milk derived from non-designated cattle which, when ingested, protects against the human-type bacillus. This is shown in figures for Jersey and for the Scottish counties with a high proportion of attested herds, where pulmonary tuberculosis has distinctly increased; whereas in the Scottish counties with a low proportion of attested herds pulmonary tuberculosis has distinctly decreased.

High Wycombe, Bucks.

L. PITCHER.

THE DENTISTS' BILL

SIR,—In 1907 a group of progressively minded privat individuals, stimulated by the late Dr. James Kerr then school medical officer to the L.C.C., started minor-ailment clinic in an old disused public-house of the Blackfriars Road. At the same time they started dental clinic, and my father, the late Frederick Breese was appointed the first dental surgeon. For about year the L.C.C. watched the new enterprise, and whe it proved itself they gave it a rather lukewarm blessin and some financial support to the committee of management.

Such was the beginning of school dentistry in London I remember vividly the many difficulties my father ha to overcome: very poor equipment at the outset, n anæsthetist, the stubborn conservatism of the parent (very Left in politics), and the fears of his small patients Very soon, by gaining the confidence of all with whom he was in contact, he laid, by his example, the foundation of what was to become a comprehensive school denta service throughout London. My father worked in thi clinic until he retired from active practice some thirt years later.

Now there are certain facts about the dental treatmen of children which should be remembered when considerin the very revolutionary change which is contemplated i the Bill at present before Parliament.

Firstly, children in a dental chair are patients, and lik adults they may be good patients or bad ones. Sometime they sit still, and at other times they fidget; or they may d both in one session, for they tire quickly.

Secondly, a dental operation, like other operations on th human body, may be a simple or a difficult procedure. What at the outset, appears to be quite a trivial matter may becom difficult literally in the twinkling of an eye. Such a chang may be brought about by the unpredictable behaviour of th child or the mood at the moment of the operator.

Another factor is the parent. Are not relatives sometime more trouble than the patient?

No doubt all these points have been taken into account by those who will have to implement this "reform" i it becomes law. They will have considered the lega aspect of responsibility for the actions of the "full trained ancillary in a limited field of dentistry." The will have blueprints ready for the necessary trainin establishments, the recruitment of the requisite teachin staff, and the supply of patients for the trainees t practise on. The appointed place in the scheme for th supervisory dental surgeon will have been settled. N doubt the training curriculum has been considered an approved, and intermediate and final examinations wil not have been forgotten. At the end of the trainin course, the ancillary, having passed the examination, wil be found fit to let loose on the child population.

Have you, Sir, asked yourself why a "fully trained person" has to work under the supervision of a qualified dental surgeon? Do State-registered nurses carry out their duties under the supervision of a physician o surgeon? Does the physiotherapist give her patient massage under the watchful eye of the director of physical medicine? Of course not, and if ever the dental ancillaries become practising deciduous dentists (for that is what is meant) all the supervising officer can do will be to select the patients they are to treat, indicate the lines that treatment is to follow, and come to the rescue if difficulties supervene—if he is on the spot and available.

It might perhaps be wiser to pause and to ask again whether this revolutionary change is in the best interest of the patients, or whether the effort might with bette advantage be directed to: (1) encouraging more entrants to the dental schools; (2) making school dentistry, for so long a Cinderella, an attractive career for the dental surgeon; and (3) emphasising the need for the prevention of dental disease.

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[1] *Lancet*, 1951, ii, 786.

auricles and ventricles. There is, however, good reason to believe that under suitable conditions an impulse which circulates within the auriculoventricular junction can effect a contraction of the auricles and ventricles every time it approaches them.[5] A circulating impulse need not necessarily traverse the auricles in order to cause their frequent action—it can stimulate the auricles en passant. It remains to be seen whether such a mechanism has any bearing on the known clinical forms of auricular tachycardia. Obviously, the question cannot be settled by applying cinematographic and electrocardiographic methods to the auricles only; it requires study of the conditions in the auriculoventricular junction. It seems that at present the latent and the manifest varieties of reciprocal rhythm offer the only support to the hypothesis connecting the "circus movement" with clinical arrhythmia.

Central Emek Hospital,
Affula, Israel.
P. FLEISCHMANN.

THE ETHICS OF LEUCOTOMY

SIR,—Dr. Mackenzie (March 29) is drawn to accuse me of framing a moral judgment because he interprets the word "faulty" in the sense of blameworthy. According to my *Webster's New International Dictionary*, this is an obsolete or rare definition of the word. The common definition given is: "containing faults, blemishes, or defects; imperfect; not fit for the use intended." Had I wished to pass a moral judgment, I would have used some such adjective as evil, wicked, or sinful.

Park Prewett Hospital,
Basingstoke, Hampshire.
I. ATKIN
Physician-Superintendent.

B.M.R. AND RADIO-IODINE TESTS IN DIAGNOSIS OF THYROID DISEASE

SIR,—In my letter (March 8) I set out to prove that there was a divergence of opinion on the respective values of radioactive-iodine uptake and the B.M.R. in the diagnosis of thyroid disease. The reply of Dr. Goodwin and his colleagues (March 22) confirms the views I put forward.

Briefly my thesis was this: (1) Keating et al.,[6] of the Mayo Clinic, and I obtain quite different results for the B.M.R. in normals and in patients with thyroid disease than do Goodwin et al.[7]; and (2) Keating et al. and Goodwin et al. do not get the same results on the radio-iodine uptake in thyroid disease.

B.M.R. range for normal people.—I repeat that no matter what standards are employed (and Goodwin et al. have not yet stated theirs) a range of −20 to +20% clearly indicates errors of technique. The distribution of deviations of the heat output (calories per square metre per hour) from the mean follows a gaussian curve, so it is unlikely that readings are *frequently* encountered at either extremes of the range.

B.M.R. range in euthyroid people.—All normal people are euthyroid (i.e., with no thyroid disease), but not all euthyroid people are normal. Goodwin et al. seem confused by this, for in their original paper they write: "with our technique *normal individuals* may give readings lying between +20 and −20 per cent," whereas in their letter (March 22) they state that +20 to −20% "is a range which from prolonged clinical use we have adopted because so frequently readings have been encountered at the extremes of this range *in indubitably euthyroid individuals*." Of course the range for euthyroid individuals is wider than the range for normal people. The euthyroid range might well be +40 to −40% (*no matter what standards*) if the cases included are of leukæmia, polycythæmia vera, the active stage of hyperpituitarism, Cushing's basophilism, heart-failure with dyspnœa, lipoid nephrosis, nephrotic Bright's disease, Addison's disease, anorexia nervosa, and malnutrition due to various causes.

The iodine diagnostic test for thyrotoxicosis.—For many years now I have been stressing the value of the effects of iodine on the B.M.R. in the diagnosis of mild thyrotoxicosis, and more recently I have advocated the use of thyroid in much the same way in the diagnosis of mild hypothyroidism. Such expedients were described in your annotation (March 8) as "somewhat clumsy," while Goodwin et al. state: "it is of little help to the clinician to be forced to use a therapeutic test with iodine to assess the meaning of a particular B.M.R." Is it a clumsy expedient to count the reticulocytes daily from the third to the tenth day in a case of macrocytic anæmia during a course of anti-pernicious-anæmia therapy, to estimate the hæmoglobin in a case of hypochromic anæmia during iron therapy, or to follow the course of a case of doubtful rheumatic fever during salicylate therapy, and the like, in order to confirm a diagnosis?

24-hour uptake of radio-iodine by the thyroid.—Goodwin et al. misquote me. It was never my intention to impute to Goodwin et al. claims they did not make. I stated that they "*can* claim from their figures that it is absolutely specific." Nevertheless my statement requires alteration in order to make it more precise. Below are the figures taken from their original paper:

	24-hour uptake of radio-iodine by thyroid, range (% dose)
Normals	19–53
Primary thyrotoxicosis	54–87
Toxic adenoma	55–76

It is seen that in both groups of thyroid toxicity there is no overlap into the normal range; and consequently from these findings it is difficult to understand why Goodwin et al. decided to agree with the views of Keating et al., who concluded that radio-iodine tests in toxic adenoma are of limited value at the best (between a third and half of their cases fell within the *normal range*).

B.M.R. results in "functional disorders."—The range reported by Keating et al. was +19±2·8%, but as I said in my earlier letter they stated that these elevated B.M.R.s were probably due to poor tests. That is also my experience. Elevated B.M.R.s in anxiety states are simply due to poor tests and the inability of the operator to obtain or recognise basal conditions.

The B.M.R. in heart-failure.—There still appears to be some confusion about the effect of heart-failure on the B.M.R. In the first place heart-failure does not raise the B.M.R. unless dyspnœa is present. The increased B.M.R. is due to the increased work of the respiratory muscles and the work of the extra respiratory muscles. The problem, which your annotation seems to be concerned with, is how to confirm a diagnosis of thyrotoxicosis in a case of thyrotoxic heart-failure when dyspnœa is present. One way would be to *treat the patient, without recourse to iodine or iodides,* until the dyspnœa had disappeared, then estimate the B.M.R. before and after iodine medication. The factor of the patient's non-thyrocardiac condition could thus be excluded as a cause of hypermetabolism.

Your annotation states that I have implied that measurement of the B.M.R. is not wholly objective, but "contains also the operator's subjective opinion that the patient was truly basal at the time of the test." I have always held those views. In this respect, measuring a B.M.R. is in no way different from, for example, taking out a stomach, auscultating a heart, or photographing barium.

London Clinic, W.1.
J. DOUGLAS ROBERTSON
Director,
Department of Clinical Investigation.

DRUG RESISTANCE OF MICRO-ORGANISMS

SIR,—The interesting letter from Dr. Banks (March 15) on the use of chloramphenicol in infections due to penicillin-resistant staphylococci prompts me to report the isolation of a relatively insensitive strain of a staphylococcus from a case of "sticky eye" in a newborn infant.

This organism was resistant to 32 µg. of chloramphenicol per ml. but showed no growth in 64 µg. per ml. The Oxford staphylococcus tested at the same time was resistant to 4 µg. per ml. and showed no growth in a concentration of 8 µg. per ml. The strain isolated was resistant to 500 units penicillin per ml.

One might perhaps point out, for the benefit of those not familiar with the disc technique, that the size of zones of inhibition due to different antibiotics depends

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5. Samojloff, A., Tschernoff, A. *Z. ges. exp. Med.* 1930, 71, 768.
6. Keating, F. R., Haines, S. F., Power, M. H., Williams, M. M. D. *J. clin.* [illegible] 1425.
7. Goodwin, [illegible] G., Miller, H., Wayne, E. J. *Quart. J* [illegible]

partly upon the quantity of antibiotics with which the discs are impregnated. The fact that certain laboratories obtain equal zones of inhibition by this method does not necessarily imply that the organisms are equally sensitive to therapeutically possible concentrations of the antibiotics concerned.

Bernhard Baron Research Laboratories,
Queen Charlotte's Maternity Hospital,
London, W.6.   R. M. CALMAN.

Parliament

The Bill in Committee

IN the motion on the Money Resolution to the National Health Service Bill on April 3, Mr. GEOFFREY BING said that the money resolution authorised the collection of new charges and provided for the money to be paid to the Treasury. Yet under clause 6 of the Bill, it seemed to him that the Government proposed to pay some of these moneys to the hospital boards instead of into the Treasury. Mr. ANEURIN BEVAN asked if a regional hospital board was entitled to use any receipts from charges made for, say, abdominal belts to be set off against the rest of their expenditures. Mr. H. F. C. CROOKSHANK replied that the present intention was that cash recovered through the appliances account will be paid into the Exchequer and will not be set off by the hospital boards. Mr. BEVAN construed this as meaning that we were starting off the year with a severely contracted hospital service or would need a supplementary estimate. Charges on appliances " will not assist the hospital authorities at all, but would automatically go to make up the £40 million for the general practitioners."

A TIME-LIMIT

The House then went into committee, and Mr. H. A. MARQUAND moved an amendment limiting the operation of the Bill to April 1, 1954. If the Bill was being introduced to reduce Government expenditure in an emergency surely we must look forward to a time when the emergency would be over. He had chosen 1954 as the time-limit because it would give the nation an opportunity to hold a grand inquest on the N.H.S. after six years' experience. Mr. ENOCH POWELL objected on the grounds that patients might be tempted by such a proviso to hold back from getting treatment in the hope that they might escape the charge. Mr. F. MESSER supported the amendment because he believed that if the N.H.S. was to be a success it must be comprehensive. The two years would give us an opportunity to see where other economies could be made. We must be clear, he said, whether the purpose of the Bill was to act as a deterrent or to save money. He did not believe people went to hospital for fun. It might be inevitable, because the nation came first, that we were for the moment unable to give treatment to all who needed it, but if so let us limit the period. Mr. ARTHUR BLENKINSOP declared that if the charges were intended to be permanent this was a change of principle and not of detail. He reminded the committee that, so far from being extravagant, we spend a far smaller proportion of our national income on health than does the United States. Mr. HORACE KING pointed out that the clause gave the Minister power to make regulations far beyond any of the charges he proposed at present. A Bill which conferred such wide powers should surely be limited to two years.

Mr. CROOKSHANK pointed out that though the Act of 1951 which dealt with appliances, including dentures and spectacles, had a time-limit, the Act of 1949, which took power to impose a charge for prescriptions on the general practitioners' patients, had no limit. Because this new Bill also dealt with prescriptions the Government had decided it was reasonable that no limitation of time should appear in this Bill either. In reply to the question whether that meant the charges were permanent he would remind the committee that they could by Order in Council vary the charges or direct that they should at any time cease to exist. He did not see why anyone should assume from this Bill that the charges were intended to be permanent. We found ourselves in a great national emergency, and this Bill was one of the means by which we were trying to rectify the home sector of the emergency. The amendment was lost by 276 votes to 263.

EXEMPTION OF OUTPATIENTS

Dr. EDITH SUMMERSKILL moved an amendment to exempt the hospital outpatient from the charge on drugs and medicines. The position of the outpatient, she held, was entirely different from that of the ordinary patient. She agreed that the drug bill was out of control, and that many people were enjoying too expensive prescriptions, but that was not the fault of the outpatient. Mr. ENOCH POWELL held that excessive pressure on the general practitioners' surgeries and on the outpatient departments of our hospitals hung together and must be dealt with together. But he felt that one of the big questions raised by the Bill was the chronic sick. He thought the right way to answer the problem was not by classifying the sickness of the patient or the resorts to which he went for treatment, but by concentrating on efficient machinery for relieving need. Miss JENNIE LEE thought the charges would be a temptation to sympathetic doctors to overprescribe to save their patients' money. She pointed out that if a prescription cost less than 1*s.* a poor patient would be unable to reclaim the money. Miss PATRICIA HORNSBY-SMITH said that the Government felt that if a charge was to be made for prescriptions it was not fair to exempt people who got their medicine from an outpatient department. There was the further difficulty that some hospitals did not have a dispensing service. If prescriptions in outpatient departments were free, pressure on hospitals would increase. The average cost of a prescription was 3*s.* 8*d.* The 1*s.* prescription was only a moderate proportion of this cost. She emphasised that if a patient thought his medicine cost less than 1*s.* he was free to buy it outside the health service. Less than 1 in every 100 prescriptions cost less than 1*s.* and most of those cost between 10*d.* and 11*d.* The amendment was rejected by 281 votes to 269.

Hospital Finance in the Newcastle Region

In the House of Commons on April 1, Miss IRENE WARD pointed out that though Newcastle upon Tyne Regional Hospital Board served a population of 2,911,922, or approximately 6·64% of the total population of England and Wales, the money, running costs and capital, allotted to the hospital service in the Newcastle region for 1951–52 was £11,266,000 for regional hospital board hospitals and £1,156,567 for the teaching hospitals. That was approximately 5·1% of the £243 million allotted to the hospital service of the whole of England and Wales. Newcastle region was therefore getting about 23% less than its proper share. Whatever might be the reasons, good or bad, which before July, 1948, left some parts of the country with a good hospital service and other parts with a bad one, there could be no justification in the National Health Service for maintaining grossly different standards. On the population basis, and with the country's present expenditure on the hospital service, Miss Ward contended that the Newcastle region should be getting about £16 million per annum instead of £12,422,000. She was grateful to the Minister for the supplementary allocations, amounting in all to £150,000, made from the underspending of other regions, but she felt the Newcastle region's basic allocation should be adjusted.

Miss PATRICIA HORNSBY-SMITH, parliamentary secretary to the Ministry of Health, pointed out that the largest part of the gross sum allocated to regional hospital boards was used for revenue and maintenance and a smaller part for capital expenditure. The revenue for maintaining existing resources for staffing, wages, laundry, food, and the like within a hospital must be related to the existing hospital resources and not to the population. If there were not the nursing staff and the hospitals grants for maintenance could not be expected. Miss Ward's claim for £16 million was unrealistic in relation to the number of hospitals in the Newcastle Regional Hospital Board's area. This year's allocation of £12,359,000 to the board included an amount for developments and improvements which was the second highest in the country. Also in that allocation was an additional £200,000 which would enable the region to refrain from closing four maternity hospitals with 63 beds, and an infectious-diseases hospital with 30 beds, and would give the board a chance to open the greater proportion of 546 beds many of which were for tuberculous patients. The amount available for capital investment programmes was severely limited at present. For 1950–51 the Newcastle Regional Hospital Board received £738,000, which included an additional allocation of £224,000; in 1951–52, with the programme drastically curtailed, they would receive a basic allowance of £384,000. The Newcastle region had 6% of the staffed beds in England and Wales, and the share of capital allocation given to them this year would be 6·8% of the capital available for regional boards.

QUESTION TIME

Cancer of the Lung

Mr. William Shepherd asked the Minister of Health if he was aware that the arsenic content of English cigarettes had been found to range twice as high as that of American cigarettes and 25 times as high as that of Turkish and Rhodesian cigarettes; and whether, in view of the fact that there were grounds for the belief that this arsenic content might be the cause of the increasing incidence of cancer of the lung, he would regulate the entry into the country of tobacco having an unnecessarily high-arsenic content.—Miss Patricia Hornsby-Smith replied: The Minister is aware that a small-scale study showed these proportions, but I understand the amounts were very small and varied widely in the same types of cigarettes. Also the Minister is advised that arsenic in tobacco smoke is not established as a likely cause of cancer of the lung, and that the great bulk of the tobacco used in British cigarettes comes from the countries mentioned in the question.

Replying to a further question Miss Hornsby-Smith stated that international lung cancer statistics gave no indication that arsenic in cigarettes caused cancer, though one Turkish hospital had reported a high incidence of lung cancer.

Cancer Publicity

Mr. Shepherd asked the Minister if he had given consideration to the desirability of education in the cancer field; and what conclusions he had reached.—Miss Hornsby-Smith replied: The Central Health Services Council have advised me that it is undesirable at the present time for any cancer publicity to be carried out by any central Government organisation direct to the general public. The Minister of Health's Cancer and Radiotherapy Standing Advisory Committee are considering the merits of local schemes of cancer education.

Dr. Barnett Stross: Will the hon. lady bear in mind that the type of advice she has been given is in the minds of many people wrong and that the public have a right to know what dangers they face? The more we know about it the better for all.

Mr. John Hynd: Can the hon. lady indicate how much of the increase in deaths attributable to cancer is due to the improvement in diagnosis?

Miss Hornsby-Smith: I would agree that there has been a considerable improvement in diagnosis in the early stages of the incidence of cancer and that has substantially contributed to the increased figures. Taking the best medical advice at our disposal we do not think it is advisable to increase public alarm. We are, however, using all endeavours by the education of general practitioners in early diagnosis to encourage all possible methods of ascertaining the incidence of this disease.

General Practitioners

In answer to a question Mr. H. F. C. Crookshank said that at Jan. 1, 1952, the number of general practitioners in Great Britain receiving payment from the National Health Service was 20,859. Mr. King: Is the Minister aware that his answer means that the Danckwerts award proposes to increase the income of doctors by £10 per week with £30 a week back money?

Mr. King further asked the Minister what sum of money was paid in 1951, under the National Health Service, to general practitioners in Great Britain.—Mr. Crookshank replied: Figures for the calendar year are not available, but for the year ending March 31, 1951, the total amount payable to general medical practitioners in Great Britain for work done under the National Health Service is estimated to have been £51,644,000. Mr. King: Is the Minister aware that his answer indicates that the average income of the general practitioner from the National Health Service is £50 per week and, while nobody would object to making up the money received by rural doctors and those with small lists, there seems no justification for the amount proposed under the Danckwerts award?

Accommodation for Permanent Invalids

Mr. J. Enoch Powell asked the Minister how many institutions existed under his control specifically for the accommodation of permanent invalids in early and middle life; and what was the capacity of these institutions.—Miss Hornsby-Smith replied: Two separate establishments with 54 beds are now in process of conversion to this use. Five other special sections of larger hospitals provide 109 beds, and three more units with 72 beds are in various stages of preparation. The number of hospital patients in this group is not large—possibly between 400 and 500 spread throughout the whole country.

Public Health

Yellow-fever Inoculations

In accordance with an international agreement, the Government of the United Kingdom can insist on the international recognition of yellow-fever inoculations performed in this country only if: (a) they are done at a centre or by a medical practitioner specifically authorised by them for that purpose; (b) the certificate is given on one of the international forms specially supplied to such centres or practitioners; and (c) a vaccine approved by W.H.O. is used for the inoculation. The centres and others so authorised have to be notified to the World Health Organisation, and the names are published by W.H.O. to all countries so that the authenticity of the certificates may be verified.

Authority to give yellow-fever inoculations is given only when the Ministry of Health is satisfied that special storage facilities for the vaccine are available and that the vaccinators are conversant with the necessary technique.

Certificates that do not comply with the above conditions will probably not be accepted by foreign health authorities; and their holders may be put to great trouble and inconvenience, and even be subject to isolation.

A list of places at which yellow-fever inoculation can be obtained free of charge will be found on the back of the notice to travellers which is issued with all renewals of passports; and this list can be obtained from travel agencies or the Ministry of Health.

Scotland's Health

The best of Scotland's health news for 1951[1] is that for the third year in succession th[illegible] tial drop in the death-rate from [illegible] which now stands at 37 per 100,000 of the population (1884 deaths) as against 66 in 1948 (3415 deaths). The incidence, as measured by notification of new cases, also continues to fall, though not so rapidly. But this is largely because the problem is being tackled at an earlier stage, and because the aim is to eliminate the disease and not merely reduce the death-rate. Even with this handicap the provisional notification-rate for 1951 is 154 (representing 7875 new notifications) as against 167 (8653 new notifications) in 1949.

Outside tuberculosis the year is described as "static." The common infectious diseases remained at a low level, the health of the school-children was well maintained, and the infant-mortality rate—37 deaths per 1000 live births—was the lowest yet recorded. The crude death-rate rose slightly, but as the increase was in the higher age-groups, and was largely due to influenza and respiratory diseases, it is held to be more a reflection of the severe weather in the early part of the year than of any deterioration in the general health of the nation.

The Scottish Health Services Council, whose report is included with that of the Department of Health, have for some time been studying the increased number of deaths due to heart-disease among people under 60 and he increased incidence of this group of diseases especially mong people under 50. Four research projects have een started on the council's recommendation.

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[1] Reports of the Department of Health for Scotland and Scottish Health Services Council, 1951. H.M. Stationery Office. 1952. Pp. 124. 3s. 6d.

Since the charges for spectacles and dentures came nto force last May, applications have dropped by about 5% for spectacles and about 30% for dentures. Ten entists have joined the school dental service, bringing he total up to 104.

VITAL STATISTICS

A preliminary report on the year 1951 by the Registrar-eneral for Scotland[1] shows that the birth-rate was 17·7 er 1000 population; this is the lowest since the late ar and equals the average for the period 1935–39. he stillbirth-rate—27 per 1000 total births—was the ame as in 1950. The death-rate of 12·9 per 1000 population was 0·5 above that for 1950. The infant-mortality ate of 37 per 1000 live births was the lowest yet recorded n Scotland; and the neonatal death-rate of 22 per 1000 as also the lowest. The maternal-mortality rate, as in 950, was 1·1 per 1000 live and still births.

Deaths from tuberculosis continued to decline. The eath-rate from all forms of this disease was 43 per 00,000 (respiratory 37, non-respiratory 6).

Northern Ireland in 1951

The Registrar-General for Northern Ireland announces hat in 1951 the death-rate from tuberculosis (45 per 00,000 population) and the maternal-mortality rate 1·1 per 1000 births) were the lowest ever recorded n the country. The death-rate increased from 11·6 per 000 population in 1950 to 12·8 in 1951, mainly owing to he epidemic of influenza in the early part of the year. he infant-mortality rate was 41 per 1000 live births. he birth-rate was 20·7 per 1000 population, thus ontinuing to fall from the 1943 peak of 24·2.

Help in Diagnosis of Smallpox

Some years ago a panel of doctors with special experience of smallpox was formed to help medical officers of ealth needing a further opinion on the diagnosis of this isease. The list of doctors on this panel has lately been rought up to date; district medical officers of health ay now also seek advice from a member of it. General ractitioners or members of hospital staffs should first all in the local medical officer of health when they have possible case of smallpox.

Variola Minor

According to provisional figures, in the week ended pril 5 new cases of variola minor in England numbered —5 at Rochdale and 1 at Chadderton (this patient had bviously been infected at Rochdale). At Rochdale there as a lull in notifications; but unfortunately some of he recent cases had not been in line of contact and a urther wave of infection was regarded as possible. At ldershot, where 1 case was reported earlier, the number f civilians exposed was very small, and the situation as believed to be well under control. In addition, ontacts remained under surveillance in relation to ases at Whitworth, Bacup, and Heywood.

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[1] Quarterly Return of the Registrar-General, Scotland, for the Quarter ended Dec. 31, 1951. H.M. Stationery Office. Pp. 40. 2s. 6d.

Infectious Diseases in England and Wales

Disease	Week ended March				
	1	8	15	22	29*
Diphtheria	33	38	53	33	29
Dysentery	647	639	642	516	592
Encephalitis:					
Infective	2	3	3	1	3
Postinfectious	1	3	..	7	3
Food-poisoning	74	94	117	127	65
Measles, excluding rubella.. ..	6234	6884	7122	6885	6953
Meningococcal infection	34	57	46	48	38
Ophthalmia neonatorum	31	46	33	54	32
Paratyphoid fever	12	6	7	6	12
Pneumonia, primary or influenzal..	1061	1143	953	848	801
Poliomyelitis:					
Paralytic	15	13	13	12	10
Non-paralytic	4	6	9	8	2
Puerperal pyrexia and fever ..	274	232	240	266	268
Scarlet fever..	1506	1581	1547	1488	1403
Smallpox	7	62	6	16	18
Typhoid fever	4	..	4	1	1
Whooping-cough	2792	2918	3091	3134	3110

* Not including late returns.

Obituary

LEONARD ERSKINE HILL

Kt., M.B. Lond., LL.D. Aberd., F.R.S.

Sir Leonard Hill, who died on March 30 at the age of 85, was a physiologist who applied his science to problems of everyday life. His versatility of mind was evident both in his researches and in his skill as a painter and imaginative writer. The complex and unusual combination of the scientific, artistic, and practical temperaments which he displayed could be attributed to his family background; for he came of a family which during the last hundred and fifty years has contributed some outstanding names to literature, law, and science. He was the son of Birkbeck Hill, the Johnsonian scholar, and a grand-nephew of Sir Rowland Hill of penny-postage fame. Rowland Hill was a great-grandson of John Symonds whose descendants included John Addington Symonds, Sir Morell Mackenzie, Compton Mackenzie, and St. Loe Strachey. The family abilities were well exemplified in Leonard Hill's own generation. His elder brother, Sir Norman Hill, was a leading legal authority on shipping; another brother, Sir Maurice Hill, was a High Court judge; and Lord Justice Scott was his cousin.

[Press Portrait Bureau

Leonard Hill was born on June 2, 1866, at Bruce Castle, his father's school at Tottenham, and was educated there and at Haileybury. The choice of University College Hospital as his medical school depended partly no doubt on his being related to Berkeley Hill, a member of its surgical staff. His career as a physiologist began almost immediately after qualifying, in Sharpey-Schafer's department at University College. He then went to Oxford as assistant to Burdon-Sanderson, later returning to the physiology department at University College. Just after the turn of the century he was appointed lecturer on physiology at the London Hospital (at that time there was no chair of physiology at the London Hospital), and he stayed there until in 1914 he was appointed director of the department of applied physiology at the National Institute for Medical Research, then situated at Mount Vernon, Hampstead.

From the first he was interested in human physiology, and it was this that impressed and inspired his students and disconcerted some of his seniors who thought that physiologists should concern themselves only with animals. With H. L. Barnard, he devised an aneroid sphygmomanometer for measuring human blood-pressure; and with various assistants and colleagues he studied the influence of gravity on blood-pressure, the differences in blood-pressure in the arm and leg, with special reference to aortic incompetence : the filtration of fluid in the eyeball; the advantages of slow and rapid decompression for divers; the elasticity of the arterial wall; and the behaviour of the cerebral circulation. Exposing themselves to unpleasant conditions in experimental chambers, he and his associates produced very useful information about the prevention of caisson disease, about carbon dioxide as a stimulus to respiration, and above all about ventilation. Flügge in 1905 had opined that the cause of the stuffiness of a badly ventilated room was not lack of oxygen, or excess of carbon dioxide, or the presence of any mysterious exhalation; but it remained for the London Hospital workers to prove that what chiefly matters in ventilation is the maintenance of suitable humidity, temperature, and movement of the air. Hill's invention of the katathermometer has been of very real help to those concerned with, for example, the ventilation of ships.

A large, jolly, cheerful man, Hill was a stimulating chief and leader, and he attracted a brilliant team of assistants who made all this work possible. Many of those who sat in his diving-bells, and breathed into his Haldane bags were later to gain eminence in medicine as well as in physiology—for example, Robert Hutchison, John Parkinson, Alun Rowlands, J. J. R. Macleod, Major Greenwood, Benjamin Moore, and Martin Flack, whose researches in the Royal Air Force were founded on these earlier investigations with Hill. He himself was one of a galaxy of teachers then giving fame to the hospital: there were Arthur Keith and William Bulloch, both close friends; H. M. Turnbull; and Treves, Dawson, and James Mackenzie in the wards. For Mackenzie's invitation to London, and also Robert Hutchison's, he was directly responsible.

It was when he joined the staff of the National Institute for Medical Research that Hill was able to give free scope to his gift for applied physiology. His work on ventilation continued, and at the same time he made a series of experiments on the action of fresh air, sunshine, and change of temperature upon the human body. Many of these were carried out at Corton, on the coast of Suffolk, where he had a country cottage in which he and his family always spent their holidays, and his experimental subjects were himself, his family, and his many friends. The complex apparatus of the laboratory is seldom applicable on the beach, but Hill was never at a loss for producing the necessary apparatus which he could use, and use accurately, on the beach or in his own cottage. The same insistence upon making observations under natural conditions took him to the Swiss sanatoria during the course of his investigations with ultraviolet light.

His scientific standing was early recognised and he was elected F.R.S. in 1900. His contributions to ventilation led to his election as an honorary associate of the Royal Institute of British Architects, and for several years he was the president of the Association of Sanitary Inspectors. He was also a member of the Navy Medical Advisory Board and of the Army Medical Advisory Board. This latter appointment dated from the 1914–18 war, when he did much research work on chemical warfare, both in this country and in France. While he was at the London Hospital he was appointed a member of the senate of the University of London, and he always took an active part in the advancement of medical education.

Besides his many contributions to medical and scientific journals, he was the author of several books, including *Caisson Sickness*, *Sunshine and Open Air*, *Physiology for Beginners*, *Manual of Physiology*, *Health and Environment* (with Argyll Campbell), *Common Colds* (with Mark Clement), and *Philosophy of a Biologist*. His *Recent Advances in Physiology and Biochemistry*, published in 1906, was a pioneer effort in applying the discoveries of the laboratory to clinical medicine. Hill not only edited it but wrote several of the sections himself, and the other contributors included Benjamin Moore, J. J. R. Macleod, M. S. Pembrey, and A. P. Beddard. He also edited, with William Bulloch, a series of "International Medical Monographs," the contributors to which included Walter B. Cannon, James Mackintosh, and Paul Fildes. How he found time for all this writing, outside his original work and his many other interests, was sometimes a mystery, even to his friends. The explanation, however, lay in a combination of his quickness of mind, his power of concentration, and his ability to work under any conditions. No matter what was going on around him, he could insulate himself and concentrate completely on what he was doing at the moment.

His artistic abilities were considerable. Indeed, at one time it was touch and go whether he became a professional artist or a physiologist. He was equally adept with oils and with water-colours, and the private exhibitions which he held in London were well received by the critics. Equally gifted were his fairy tales for children, which showed an intuitive understanding of the child mind. A friend writes:

"The artistic and scientific temperaments are often incompatible, but in Leonard Hill they attained an almost uniquely happy synthesis which, combined with his humanitarianism, was the secret of his outstanding contribution to medicine. Throughout it all there ran a strain of childlike innocence and wonder. He was very tolerant of human foibles, but he could not tolerate what he considered pomposity or affectatio Misfortune or ill-luck in others always called out the deepe sympathy in him, but anything resembling dishonesty character roused him to anger. He could never understa what he described as the 'mysticism' of Sherrington, b the beauties of Nature were a perpetual joy. By a curio coincidence his last published contribution was a letter the *Listener* (March 27) on 'mystery of mind and brain' which he gave his reasons for disagreeing with Sherrington 'mystic view of mind.' This was published only a few da before his death, and the final paragraph aptly sums up h own philosophy: 'There is no lack of mystery in the univer as shown by the physicist, the astronomer and the biologis and the brain is capable of investigating the mystery and spreading poetry and delight.'

As we laid him to rest in the churchyard at Corto within sight of the cliffside cottage in which he had spe so many happy holidays, amid the scenes which he h painted with such loving skill and to which he had return to end his days, one realised that this was the perfect endi for the devotee of the open air, the lover of sunshine, who lasting memorial will be the healthy youth of today and the future who, largely through his pioneer efforts in harnessi physiology to the service of the community, had attained th healthiness of body and mind which is achieved by an ope air life."

Sir Leonard Hill married in 1891 Janet Alexande who survives him with two daughters and four son one of whom is Prof. A. Bradford Hill, D.SC., direct of the Medical Research Council's statistical researc unit. He was knighted in 1930.

DR. G. M. FINDLAY

R. R. W. writes: I first worked with Dr. Findlay 1942 when he was consulting physician to the We African Command, and his many interests centred roun the large research laboratory which he had fostere At that time, before penicillin was in general suppl he was making his own crude preparation and treatin yaws with it. He was a tireless worker and the fortuna possessor of a brain which on being shown a few tre could visualise the whole forest with a fair degree accuracy. During this time he directed a mass treatme operation on the 82nd West African Division for schist somiasis contracted a few weeks before sailing for Burm and he investigated a typhus epidemic in norther Nigeria. During both of these ventures the work hand was interwoven with visits to local hospitals an native markets, and Findlay, who was a non-smoke and almost a non-drinker, would exhaust many a mes by indulging in long walks in search of snails or othe material immediately after a considerable plane or ca journey.

Many of his West African colleagues were employe as abstractors in the early issues of *Abstracts of Worl Medicine*. His real love, however, was research an soon, aided by grants and the kindness of Professo Buttle, he established a laboratory at the School o Pharmacy at Bloomsbury Square. Here he worke in the lunch hour and again after tea. He was never downhearted when his experiments failed. Such temporary reverses made him the more optimistic. Not content with this double job he continued writing as prodigiously as he had done for years. My last memory of him was sitting at his desk at the B.M.A. with papers piled to the ceiling and books and manuscripts strewn all over the floor. However busy, he was always pleased to help, encourage initiative and to take on more work. If a man was ever killed by over-work surely he was.

P. C. C. G. writes: A change of wording made by you in my obituary of Brumpt (*Lancet*, 1951, ii, 1043) passed unnoticed by me in the proof, but I should be grateful if you would allow me to quote the original reading. I wrote "he was a French savant of the grand tradition, and unlike the majority who rarely left their country, he exercised a world-wide personal influence because of his extensive travels." You changed this to "unlike many of his colleagues. . . ." My comparison was to the classical savant of the *Sorbonne*; Brumpt's own colleagues have travelled as extensively as he himself, and the last thing I wanted to imply was that their influence was in any way negligible.

Notes and News

CENTRAL MIDWIVES BOARD

THE following have been appointed as members of the reconstituted board for the next three years.

Appointed by the Minister of Health.—Miss G. M. GODDEN, O.B.E., S.R.N., S.C.M., matron, Hammersmith Hospital; Miss V. R. SHAND, S.R.N., S.C.M., M.T.D., supervisor of midwives, Lancashire County Council; G. T. MILNE, assistant secretary, Ministry of Health; J. A. SCOTT, O.B.E., M.D., medical officer, London County Council; J. G. THWAITES, M.B., general practitioner, Brighton; ARNOLD L. WALKER, F.R.C.O.G., consulting obstetrical surgeon, City of London Maternity Hospital (chairman).

Appointed by the Royal College of Physicians.—ALAN MONCRIEFF, M.D., F.R.C.P., Nuffield professor of child health, University of London (vice-chairman).

Appointed by the Royal College of Surgeons.—A. M. CLAYE, F.R.C.O.G., professor of obstetrics and gynæcology, University of Leeds.

Appointed by the Royal College of Obstetricians and Gynæcologists.—VICTOR LACK, F.R.C.O.G., obstetrical and gynæcological surgeon, London Hospital.

Appointed by the Society of Medical Officers of Health.—J. M. GIBSON, O.B.E., M.D., M.O.H., Huddersfield.

Appointed by the Royal College of Midwives.—Miss M. I. FARRER, S.R.N., S.C.M., M.T.D., matron, St. Mary's Maternity Hospital, Croydon; Miss C. K. KNOTT, M.B.E., S.R.N., S.C.M., chief nursing officer, Salvation Army; Miss E. J. MERRY, S.R.N., S.C.M., general superintendent, Queen's Institute of District Nursing; Mrs. E. WALKER, S.R.N., S.C.M., supervisor of midwives, Newcastle upon Tyne.

Appointed by the County Councils Association.—A. ELLIOTT, M.D., M.O.H., Kent.

Appointed by the Association of Municipal Corporations.—Alderman F. E. TYLECOTE, M.D., F.R.C.P., professor emeritus of medicine in the University of Manchester.

MEDICAL REGISTER

THE Medical Register for 1952 contains 82,256 names of doctors, an increase of 2034 (almost double the preceding year's increase), although the new registrations were 85 less than last year's and 31 less than the average for the last ten years. The Commonwealth list has decreased (by 46) for the first time since 1945; and the foreign list has gone on decreasing—by 28 to 71. The Register is published for the General Medical Council, 44, Hallam Street, London, W.1, by Constable & Co. Ltd., 10, Orange Street, W.C.1. It is in two volumes and costs 48*s*.—an increase of 6*s*.

University of Cambridge

On March 22 the following degrees were conferred

M.Chir.—William Waugh.
M.B., B.Chir.—G. B. Davison, *M. P. Ward.

* By proxy.

University of Glasgow

On March 25 the degree of M.D. was conferred, in absentia, on N. McE. Lamont.

Irish Conjoint Board

On March 28 the following, having passed the final examination of the board, were admitted to the licentiateship of the Irish Royal Colleges:

Sita Bephia Bissessar Boodhoo, L. B. Burke, J. H. Burns, B. J. Dolan, J. D. Drennan, B. M. Duncan, J. J. Fahey, G. M. FitzGibbon, Mary B. Gilmartin, Carmel M. Granville, Mary T. Healy, T. A. Mulligan, J. G. McCaffrey, K. A. W. Overton, E. W. O. Thomas.

Wright-Fleming Institute of Microbiology

The Earl of Iveagh will preside at the inauguration of the memorial to Sir Almroth Wright which is being held at the institute, St. Mary's Hospital, London, W.2, on Wednesday, April 30, at 5.30 P.M. Dr. John Freeman will give an address.

X-ray Mirror for Dental Fluoroscopy

The Ministry of Health states that its attention has been drawn to the potential dangers in using an X-ray mirror for fluoroscopic dental examination which is on sale in this country. The Ministry is advised that this instrument is potentially hazardous to the operator, the assistant, and the patient.

Royal College of Surgeons of England

At a meeting of the council on April 3, with Sir Cecil Wakeley, the president, in the chair, it was announced that the college had been adjudged by the House of Lords to be a charity, in a case arising out of the will of the late Lady Bland-Sutton.

Mr. I. B. Jose, of Adelaide, vice-president of the Royal Australasian College of Surgeons, was elected a temporary member of the court of examiners.

Mr. G. T. W. Cashwell was elected to the fellowship of the college ad eundem. The following were elected to the fellowship without examination as being medical practitioners of at least 20 years' standing: Mr. E. H. Shaw, Mr. S. A. Henry, Mr. V. B. Green-Armytage, Sir William Kelsey Fry, Mr. A. J. Boase, and Prof. J. Kirk.

The Jacksonian prize for 1951 was awarded to Mr. Rodney Smith, and a certificate of honourable mention was awarded to Mr. Oliver Jelly. The council selected the following as the subject for the Jacksonian prize for 1953: Pathology and Surgery of Peripheral Vascular Occlusion. The John Hunter medal and triennial prize were awarded to Dr. Cuthbert E. Dukes for his contributions to pathology in general, with special reference to his work on cancer.

A Leverhulme research scholarship was awarded to Mr. J. N. Ward-McQuaid, and Mr. D. I. Williams's Leverhulme scholarship was renewed for a further year.

Diplomas were granted jointly with the Royal College of Physicians as follows:

D.T.M. & H.—M. A. Baddoo, K. L. Batten, R. A. Benninger, Bryan Bevan, Corrado Bianchini, Elizabeth R. Bridgman, P. A. Cooper, R. E. Davenport, Tadeusz Derola, E. M. Ensor, J. G. Grounds, N. R. Gupta, C. R. Jones, V. N. Kapur, S. A. Karimjee, K. B. Kenyon, P. K. K. Knudsen, A. H. Laxton, G. S. Mahapatra, M. G. Mandavia, Dirk Metselaar, Declan O'Keeffe, J. G. Paranjpe, R. F. Payne, M. A. A. Razek, H. A. Reid, L. R. Roberts, Kathleen C. Rogers, Jacob Schneider, F. D. Schofield, B. M. A. Shafik, P. A. Shave, Swasdi Skulthai, Chanvitya Sudhipongse, W. R. G. Thomas, W. R. W. West-Watson.

D.O.—J. D. Brosnan, P. A. Clarke, R. R. Collmann, Teresa Coyle, Gwenllian Edwards, W. S. Foulds, Peter Griffiths, J. W. Hornbrook, E. G. Hurd-Wood, A. S. Jones, S. B. Kapur, J. K. McCall, B. M. McOwan, R. J. Patel, Rhona A. Reid, C. W. Thornhill, Dorothy F. Usher, M. P. van Huyssteen, C. H. Walsh.

D.Phys.M.—D. C. Arnott, L. B. Blomfield, Joseph Fulton.

D.C.H.—Anne M. Allen, J. D. Allen, Marion M. Ashforth, Honor E. Bambridge, Alice Benjamin, D. U. Bloor, D. S. N. Brierley, J. G. S. Buchanan, G. J. Budow, June D. Cain, W. H. Cary, Pincus Catzel, Rachel Chacko, Jean E. H. Charlton, Debendra N. Chatterji, P. R. Clay, Nancy Cole, S. V. Cullen, Lorna C. Davies, Sheila F. Dawson, D. J. Dobson, S. E. Ellison, R. J. Fassina, Mary E. G. Feetham, B. M. Fohler, Albert Freedman, Serem Freier, Louis Friedlander, N. A. W. Gibson, Nochem Goldblatt, Irene Harrison, M. M. Hassan, J. P. de V. Hendrickse, Susan E. Herdman, Catherine M. Hoyle, T. T. S. Ingram, Brenda James, E. H. Judge, S. M. Kaplan, Irene E. Kenmuir, Margaret M. Kerr, D. K. Konyoumdjian, Janet M. Lamont, S. G. Loh, G. M. Lurie, Isabel M. McCullough, Bridget M. V. McGettigan, Mary B. B. McGregor, Kathleen G. McKee, Elizabeth Monkhouse, N. M. Newman, G. A. Perling, H. T. Phillips, Dorothy E. M. Pierce, Jill Poole, Megan C. Pratt, D. H. H. Pullon, H. G. Rischbieth, Margaret Rogers, N. R. Rowell, Olive Sharpe, Freda Sheinbaum, Nathan Sher, Joan Slack, A. L. Speirs, F. A. Springall, Harry Stein, Janet M. Stokes, Hilda J. Tanner, J. B. Taylor, R. M. Thomson, Sheila M. Tyrrell, Sam Vakil, H. K. Virik, J. R. H. Watson, J. N. Wattie, Hebe F. Welbourn, R. H. R. White, Constance M. Wilkinson, Olive C. Wilks, Mary E. S. Wylie, V. C. G. Yzelman.

Whitley Councils

The postal address of the management side secretaries of the Whitley Councils for the health services is now 14, Russell Square, London, W.C.1. Letters to the Ministry of Health on remuneration and conditions of service of health service staffs should still be addressed to the Ministry at Savile Row, London, W.1 (telephone no. for both, Museum 6811). From April 21 the address of the mental health division will be the Ministry of Health, Savile Row, London, W.1 (telephone Regent 8411).

Naval Medical Compassionate Fund

A meeting of the subscribers of this fund will be held at 3 P.M. on Thursday, April 24, at the Medical Department of the Navy, Queen Anne's Mansions, London, S.W.1, to elect six directors of the fund.

Safety in the Electrical Industry

During the course on this subject which is being held at Burton Manor Residential College for Adult Education, one day, Tuesday, April 29, is to be spent discussing the effects of electricity on human beings. A limited number of doctors are invited to join the course as non-residents for this day. The speakers will include Prof. S. Jellinek. Further particulars may be had from the warden, Burton Manor, Burton, Wirral, Cheshire.

Board of Control

On April 21 the board will move to the Ministry of Health building at Savile Row, London, W.1 (telephone Regent 8411).

Osler Club

At a meeting of this club to be held on Friday, April 18, at the Wellcome Research Institution, Euston Road, London, N.W.1, at 7 P.M., to commemorate the quincentenary of Leonardo da Vinci, Dr. K. D. Keele will speak on Leonardo the Physiologist, Dr. Ivor B. Hart on Leonardo the Physicist, and Mr. Cecil Gould, of the National Gallery, on Leonardo the Artist.

Medical Association for the Prevention of War

This association is holding a conference at the Royal College of Surgeons, Lincoln's Inn Fields, London, W.C.2, on Saturday and Sunday, May 10 and 11, to give doctors an opportunity to discuss the responsibilities of the profession in face of the threat of war. Prof. F. G. Gregory, D.SC., F.R.S., will give the opening address at 2.30 P.M. on the 10th, on the Misuse of Science. Other speakers will include Dr. M. R. Pollock, Dr. J. H. Humphrey (Biological Warfare), Mr. J. C. Flugel, D.SC., Prof. L. S. Penrose (Psychology of War Preparation), Dr. Elizabeth Topley (International Medical Services), and Dr. D. G. Leys (the Hippocratic Oath and the Declaration of Geneva). Admission is by ticket obtainable from Dr. Arnold Klopper, 24, Lansdowne Road, W.11.

The Remains of William Harvey

William Harvey was born at Folkestone in 1578, and the anniversary of his birth was celebrated there on April 1. After the ceremony the mayor of Folkestone asked medical and civic representatives to discuss a proposal to remove Harvey's remains from their present resting place in the church of Hempstead in Essex. The church is in a very bad state of repair and there is little hope of restoring it. The Harveian Society of London, whose president, Dr. J. W. Barnett, spoke at the meeting, have discussed the difficulties of restoration with those interested, but it has proved impossible to raise the large sum of money needed. The only solution seems to be to transfer the remains to another place. Alternatives suggested were Canterbury Cathedral, Folkestone Parish Church, Westminster Abbey, and St. Bartholomew's Hospital, London. The Bishop of Colchester, in a letter read to the meeting, said that he would oppose the removal of the sarcophagus from Hempstead, and that he had heard that Harvey was buried there at his own wish. If this were so it put an end to the matter. Dr. Barnett said that there was no mention of Hempstead in Harvey's very detailed will. A resolution was passed recommending that the remains be moved to a more appropriate resting place.

CORRIGENDUM.—The late Prof. Edwin Bramwell, whose obituary we published on April 5, married Miss Elizabeth Cumming Cunningham, daughter of the anatomist, Prof. D. J. Cunningham, F.R.S.

Births, Marriages, and Deaths

BIRTHS

BODMAN.—On March 26, at Hillingdon, the wife of Dr. R. I. Bodman—a daughter.

COIGLEY.—On March 28, in London, the wife of Dr. M. H. F. Coigley—a son.

NEWSAM.—On March 28, in London, the wife of Dr. J. E. Newsam—a daughter.

REID.—On April 2, in Dublin, the wife of Dr. Alistair Reid—a daughter.

MARRIAGES

MANSEL-JONES—DAVIES.—On April 2, at Wood Green, North London, David Mansel-Jones, M.B., to Mair A. Davies.

DEATHS

BOYDE.—On March 29, Harry Caine Boyde, M.B. Lond., aged 48.

FREUDENTHAL.—On March 27, in London, Walter Freudenthal, M.D. Breslau, aged 58.

GLEAVE.—On March 31, Humphrey Hart Gleave, M.B. Leeds, M.R.C.P.

HILL.—On March 30, at Corton, near Lowestoft, Sir Leonard Erskine Hill, M.B. Lond., LL.D. Aberd., F.R.S., aged 85.

Diary of the Week

APRIL 13 TO 19

Tuesday, 15th

ROYAL EYE HOSPITAL, St. George's Circus, S.E.1
5 P.M. Prof. Arnold Sorsby: Genetics in Ophthalmology.

Wednesday, 16th

ROYAL EYE HOSPITAL
5.30 P.M. Mr. Howard Reed: Visual Fields.
UNIVERSITY OF GLASGOW
4.30 P.M. (Chemistry Department.) Dr. William Pickles: E demiology [illegible] (Noah Morris lecture.)
ROYAL SOCIETY OF [illegible] Street, W.1
8.15 P.M. *Section* [illegible])r. N. B. Eastwood: L Backache.

Thursday, 17th

ST. GEORGE'S HOSPITAL MEDICAL SCHOOL, Hyde Park Corner, S.
5 P.M. Dr. J. H. Paterson: Neurology [illegible]
LONDON ASSOCIATION OF THE MEDICAL WO
8.30 P.M. (Royal Free Hospital School [illegible] Street, W.C.1.) Lady Jefferson: Last ?
ASSOCIATION OF SURGEONS OF GREAT BRITAIN AND IRELAND
9 A.M. (University College, Cathays Park, Cardiff.) Opening three-day annual meeting.
HONYMAN GILLESPIE LECTURE
5 P.M. (University of Edinburgh.) Mr. Maurice Ewing: W Resection in Cancer Surgery.
UNIVERSITY OF ST. ANDREWS
5 P.M. (Medical School, Small's Wynd, Dundee.) Prof. A. Boyd: Diagnosis and Treatment of Arterial Disease in Lower Extremities.
OPHTHALMOLOGICAL SOCIETY OF THE UNITED KINGDOM
10 A.M. (Royal College of Surgeons of Ireland, Dublin.) Open of three-day annual congress.

Friday, 18th

ROYAL SOCIETY OF MEDICINE
4.30 P.M. *Section of Epidemiology and State Medicine.* Dr. W. Cockburn, Dr. R. E. O. Williams, Dr. O. M. Lidwe Spread of Infection in Families.
8.15 P.M. *Section of Radiology.* Dr. T. Lodge: Cysts of the Lun
FACULTY OF RADIOLOGISTS
2.15 P.M. (Royal College of Surgeons, Lincoln's Inn Fields, W.C. Dr. George Simon: Lateral Position in Chest Tomogra Dr. G. Brian Locke: Carcinoma of the Middle-lo Bronchus.
BIOCHEMICAL SOCIETY
11 A.M. (University of Liverpool, Liverpool, 3.) Scientific pape

Appointments

PARRY, T. E., M.B. Manc., M.R.C.P.: consultant pathologi Llandough Hospital.

SHRIGLEY, J. A., M.B. Manc.: asst. pathologist, group laboratory [illegible] naih duties at Christie Hospital a [illegible] nchester.

[illegible]: asst. M.O.H., Warwickshire.

[illegible] D.M.R.D.: asst. radiologist, Wig

East Anglian Regional Hospital Board:

COOK, L. N., M.B. Glasg.: senior registrar in psychiatry, Norwi mental hospitals.

CROSSE, GEORGE, M.B. Madras, D.P.M.: asst. psychiatr (S.H.M.O.), Ipswich child-guidance clinic.

SOUTHERN, E. M., M.R.C.S., M.R.C.O.G.: senior registrar gynæcology and obstetrics, United Norwich Hospitals.

WORKMAN, J. M., B.M. Oxfd: medical registrar, Ipswich San torium.

Essex County Council:

CLARK, ANN, M.R.C.S.: asst. county M.O.H., North-East heal area.

DASTUR, SHIRIN, M.R.C.S.: asst. county M.O.H., Leyton heal area.

LISTER, JEANNE, M.B. Lond.: asst. county M.O.H., Dagenha health area.

Liverpool Regional Hospital Board:

BARR, S. J., M.B. Belf., F.R.C.S.E., M.R.C.O.G.: consulta obstetrician and gynæcologist, Walton Hospital.

JONES, N. B., M.B. Lpool, M.R.C.P.: consultant physician, S Helens and District H.M.C. group.

KULKE, WILLIAM, M.RAD. Lpool, D.M.R.T.: consultant radi therapist, Liverpool Radium Institute.

McKENDRICK, C. S., B.A., M.B. Camb., M.R.C.P.: consulta [illegible] General Hospital, Liverpoo

F [illegible]: consultant child psychi [illegible] r Hey Children's Hospita Liverpool.

Western Regional Hospital Board:

[illegible] M.B. Glasg., D.A.: consultant anæsthetist

[illegible] B. Glasg., D.A.: consultant anæsthetist

IRWIN, DAVID, M.B. Glasg., D.P.M.: asst. psychiatrist, Hartwoo Mental Clinic and associated clinics.

WATSON, R. T. B., M.B., B.SC. Glasg., D.P.H.: asst. tuberculosi physician to area tuberculosis physician, Lanarkshire.

The Terms and Conditions of Service of Hospital Medical an Dental Staff apply to all N.H.S. hospital posts we advertise, unle otherwise stated. Canvassing disqualifies, but candidates may normall visit the hospital by appointment.

MEDICAL RESEARCH COUNCIL NATIONAL TUBERCULIN SURVEY 1949-50

Background and Methods of Survey

At the beginning of 1949, in accordance with proposals from the Research Committee of the British Tuberculosis Association, the Medical Research Council undertook a survey to determine the prevalence of natural tuberculous infection in England and Wales. A Tuberculin Survey Committee, with representatives from the British Tuberculosis Association, was appointed to direct the Survey. It had the following members:

Prof. F. R. G. Heaf (chairman), Prof. Robert Cruickshank, Dr. W. Pointon Dick, Dr. Norman England, Dr. P. D'Arcy Hart, Prof. A. Bradford Hill, Dr. J. V. Hurford, Dr. J. E. A. Underwood, Dr. G. S. Wilson, and Dr. Marc Daniels (secretary).

Dr. A. E. Brown was appointed to coördinate the practical work of the Survey. All the field work was done by doctors and staff of the health authorities in the areas selected. Dr. Daniels analysed the results and prepared the report for the committee.

Previous surveys of tuberculin sensitivity in this country had been limited either by the age-group or by the nature of the community surveyed. There had never previously been a survey on a national scale, which could give a picture of the prevalence of tuberculous infection in the country in general and at the same point of time. The use of B.C.G. vaccine has now been introduced, and it was possible that at some time in the future anti-tuberculosis vaccines might be widely used; if this were to happen, it would no longer be possible to measure by the tuberculin test the prevalence of natural tuberculous infection in the community. It was important, therefore, to make a survey on a national scale, covering areas judged to be sufficiently representative of the country as a whole, and to do this with reasonable dispatch. A period of twelve months was fixed as a time-limit.

It would not have been possible for a single team to complete work on the scale proposed in so short a time, and it was therefore decided to ask the regional and local authorities of the selected areas to do the work through their own staff.

SELECTION OF AREAS

The committee originally decided that a list of 20 areas such as the following would be reasonably representative of different parts of the country:

Urban areas: the county boroughs of Birmingham, Hull, Leeds, Norwich, Oxford, Portsmouth, and Stoke-on-Trent; an industrial town in Lancashire; 4 boroughs of the London area; and a Welsh town.

Mining areas in Durham and Wales.

Rural areas of Cambridge, Lancashire, Northants, Somerset, and Wales.

In some of the selected areas it was found, however, after discussion with the local health authorities, that a survey would be impracticable for various reasons, the most important of which was the lack of staff to carry out the work within the time proposed. Other areas were substituted, and 2 more added, and the Survey was completed in the following 22 areas (shown on the map in fig. 1):

Urban areas: Birmingham, Hull, Leeds, Oxford, Portsmouth, Preston, Stoke-on-Trent, 4 boroughs of the London area (Fulham, Southall, Southwark, and Willesden), and the Welsh town of Newport (Mon.).

Mining areas: Durham and Maesteg.

Rural areas: Berkshire, Cheshire, Devon, Kent, Norfolk, Notts, and Montgomery. An area in the Calder Valley of Yorkshire, which was proposed as a rural community, is in fact a group of industrial communities in a rural setting; in the presentation of results it is grouped with the urban areas, as are also the two mining areas.

A brief description of the areas surveyed is given in Appendix A. It will be seen that the "rural" areas include some districts which are administratively "urban."

AGE-GROUP: NUMBERS REQUIRED

The age-group 5–20 was selected. It was held that, in view of the relatively low infection-rate in children under 5 years of age, the considerable additional organisation needed to examine adequate numbers of this group was not justified. Similarly the great majority of adults over 20 were likely to be tuberculin-positive, and it would have been difficult to recruit in a short time sufficient numbers to be tested.

The aim was to examine in each area at least 250 persons at each year of age, so as to get results which could be considered significant for each age period. A total of 4000 would therefore be needed in each area.

Because of National Service obligations it was from the outset realised that it would be hard to find adequate numbers in the male age-group 18–20. An approach was therefore made to the Army authorities, who agreed to arrange for tuberculin testing of several thousand recruits aged 18–20; this was successfully done. A similar arrangement was made for young women in the W.R.N.S., but unfortunately the number available for testing (162) was too small to warrant their inclusion in this report.

CHOICE OF TUBERCULIN TEST

The object of the survey was to determine, by means of the tuberculin test, how many persons within each age-group had previously had a tuberculous infection. This could not be determined absolutely; some previously positive might, in the absence of further infection, have lost their hypersensitivity, and some might be in the pre-allergic state. With these limitations, the test or tests used should, by giving the numbers tuberculin-positive, afford a close approximation to the numbers previously infected.

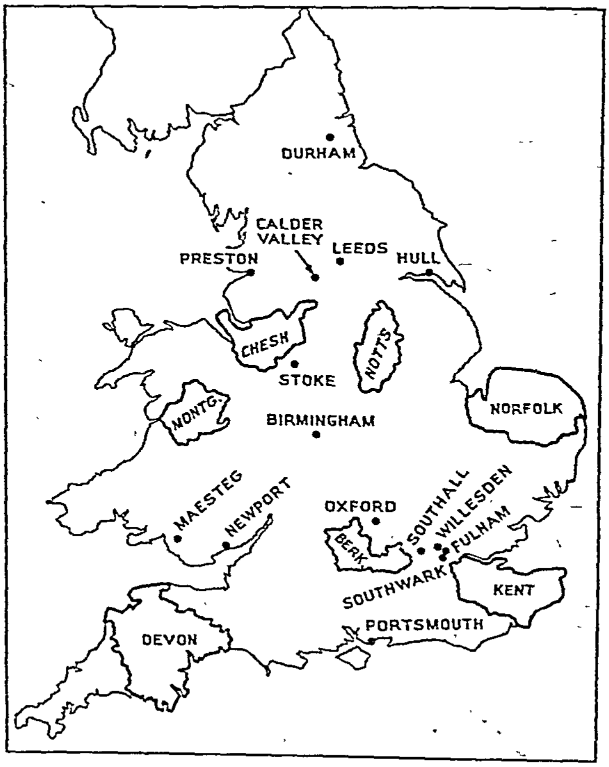

Fig. 1—Areas surveyed in Medical Research Council's national tuberculin survey 1949–50.

Age-group 5–14

Over 7000 children at each year of age were examined. In nearly every area there were over 100 boys and 100 girls at each year of age; in some there were more than 200.

The totals examined in this age-group are therefore very satisfactory; there are also some indications that they are likely to be a reasonably representative sample. In areas with a relatively small population the parents of all the children from primary and secondary modern schools in the area were approached for consent to skin-testing of their children. In Fulham, Oxford, Portsmouth, Southall, Southwark, Willesden, Calder Valley, Hull, Maesteg, and Newport schools were selected which the local education authority regarded as representative for the area, and all the parents were approached. In Birmingham, Leeds, and Stoke schools were selected, and within those schools suitable numbers of children were then selected at random; and their parents were approached. In Preston the parents of a randomly chosen sample of all the children (1 in 4) were approached. The consent-rate in these areas varied considerably, from as low as 63% in one area up to 97% in another; but it was over 80% in 10 of the 19 areas for which such figures were available. As a test of the sample, figures were obtained in some areas concerning the proportion of children receiving free school meals:

Percentage of children receiving free school meals

	Schools in the survey	*All primary and secondary modern schools in the area*
Oxford	4·2	3·5
Southall	0·7	0·8
Southwark	5·1	5·1
Hull	2·5	3·8
Devon	9·5	5·4

Though the methods of selection and the consent-rate varied, and though it is impossible to provide any precise measure, it seems probable that the children tested were a fairly representative sample of the school population.

Age-group 15–20

It was not, on the other hand, possible to undertake any methodical sampling of young people aged 15–20. Since most young people in this age-group have left school and are out at work, the intention was to seek groups in large or small workshops and in youth organisations rather than in schools or universities. As would be expected, the sampling was in some areas much less successful than obtained at the younger school ages. In some areas it was impossible, for one reason or another, to examine other than school and university groups; thus in Leeds, Newport, and Montgomery nearly all the young people examined were at school or university, and this applies also to males in Hull. There were also exceptionally large numbers from schools in Oxford and Maesteg (males and females) and in Portsmouth and Kent (males).

In some urban areas where it was possible to examine factory groups, those examined may have represented a fairer sample of the community, though the consent-rates were much lower than in the schools. On the other hand, in rural areas those examined were certainly not representative, for young people engaged in farming were not available, the response from youth clubs was negligible, and in two areas (Cheshire and Notts) the whole of the group examined were from a factory in a town in or near the area surveyed.

The proportions, of the totals examined, who were in school or university are shown for each age-group in table IA. They show, in the three broad regional groups used, that at the age of 15 the proportion from schools is 63–79%, but that in succeeding years it falls rapidly; the only high figures at ages 19 and 20 are for males in the group of urban areas other than in South England, and are due almost wholly to figures for Leeds and Hull, where university students (nearly all non-medical) were examined. It may be noted also that at ages 15–17 the highest proportion of school participants is in the rural areas; and that in almost every instance the proportion is higher in males than in females.

TABLE IA—PERCENTAGE OF TOTALS EXAMINED AT AGES 15–20, WHO WERE AT SCHOOL OR UNIVERSITY

Area	Sex	Age (years)					
		15	16	17	18	19	20
Urban England (south of Rugby)	M	65	40	29	18	10	2
	F	63	32	16	7	3	6
Urban England (North and Midlands) and Wales	M	71	42	34	21	32	32
	F	66	40	27	16	13	10
Rural England and Wales	M	77	54	43	9	1	0
	F	79	50	26	7	0·5	0

TECHNIQUE OF ANALYSIS: GEOGRAPHICAL GROUPING

Non-completed Tests

A test was considered completed if

(i) the result of the first test was positive; or

(ii) the result of the first test was negative, a second test to 100 T.U. was carried out, and the result of this second test was recorded.

An analysis was made to see if it would be necessary to make allowances for non-completed tests. The following example from one of the areas was taken as having a relatively high proportion of non-completed tests and a high proportion of positives who were positive only to the second test:

Completed tests: 206	Positive 1st test	..	38	35·9% positive
	„ 100 T.U.	..	36	
	Negative	..	132	

Of the 168 negative to the first test, 36 (21·4%) were positive to the second test, 100 T.U.

27 persons, negative to the first test, did not have a test to 100 T.U. recorded. If they are assumed to be similar to those who had a second test, 21·4%, or 6, would have been expected positive at the second test. Inclusion of these expected results of non-completed tests would then give:

Positive 1st test	.. .. ..	38	34·3% positive
„ 100 T.U.	.. .. ..	42	
Negative	.. ..	153	

Because of the small difference between 34·3% and 35·9% positive, no adjustment of the results has been made, and results of non-completed tests have been excluded.

Degree of Sensitivity

The analysis presented in this report does not include a breakdown of results according to whether persons were positive to the first or the second test. It was very soon found that between the different areas there was considerable variation in the proportion of positive reactors who were positive to the first test. Over 30 different doctors had performed these tests; and, though an attempt had been made, as previously stated, to establish uniformity of technique, this did not prevent variations from occurring and from being as great as from 52% in one area to 95% in another. The differences are, in fact, greater than could be expected to result from true differences in level of sensitivity in the various areas concerned. It had not been expected that the variations would be so great, though no doubt the vigour with which the skin was rubbed with flour-paper to prepare for the jelly test could differ considerably.

The main cause for concern in these variations was lest, in those areas with a relatively high proportion of positive reactors positive to the first test, there might be an important number of "false positives"—through the reading of scratch marks as positive reactions. Two areas in which the technique was known to have been uniform and reliable were therefore taken as a standard. It was found that the main deviation from this standard ras towards "under-reading"—i.e., missing positives o the first test—with the result that greater numbers rere submitted to the second test. Analysis of the areas 1 which the opposite tendency—i.e., "over-reading" f the first test—was manifest showed that, with one xception, the tests had been made after December, 950, when a second batch of P.P.D. was used for the jelly. 'he indications are that this batch was stronger than he first.

Further considerable variations were found in the eported proportion of large reactions to 100 T.U. In one rea no reactions were recorded with a diameter over 5 mm.; in others the diameter of positive reaction was ften recorded as over 20 mm.

In view of these technical variables it was decided to ase the analysis on the total positives, regardless of hether persons were positive to the first or the second est. (An additional analysis was, however, made, taking nly results positive to the first test; the general trends rere not different from those given in the present report.) 'he percentages of children who were positive only to 00 T.U. are set out below for grouped areas.

eographical Grouping

The indication that there were probably considerable lifferences in technique led to the conclusion also that ot too much importance should be attached to minor lifferences between different areas. In the analysis, to educe the effect of technical variables the areas were ombined in larger geographical groups; the following rouping has been used for much of the analysis:

Urban England (south of Rugby): Fulham, Oxford, 'ortsmouth, Southall, Southwark, and Willesden.

Urban England (Midlands and North) and Wales: Birningham, Calder Valley, Durham, Hull, Leeds, Maesteg, Newport, Preston, and Stoke.

Rural England and Wales: Berkshire, Cheshire, Devon, ent, Montgomery, Norfolk, and Notts.

These will be referred to as the South urban, North rban, and rural groups (though the "North urban" roup includes areas in the Midlands and in South Wales).

Results of Tuberculin Tests

RESULTS IN THREE GEOGRAPHICAL GROUPS—ALL PERSONS

The figures for the three geographical groups are given in table II and represented graphically in fig. 2. The percentage positive given for each geographical group is the unweighted mean of the percentages for the several areas in the group. This method has been adopted in preference to totalling the numbers tested and the numbers positive in each geographical group—i.e., the weighted mean—because of the variations in the total numbers in different areas (see table I). There is in fact little difference between the results of the two methods, except for rural areas at ages 17–20.

Above the age of 14, the results have been tabulated in 2-year groups to reduce the fluctuations due to small numbers. This analysis excludes results for the Calder Valley because figures for completed tests are not available for the age-group 15–20 in that area.

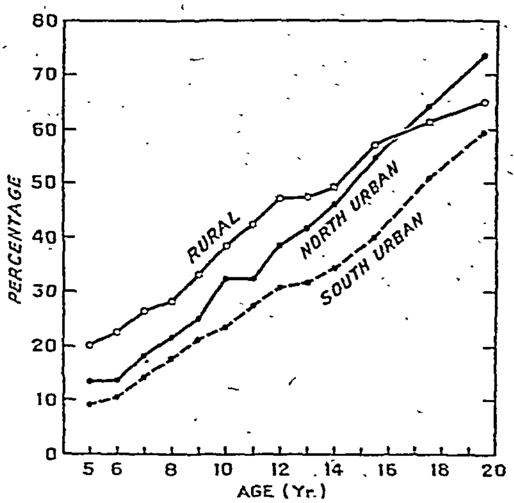

Fig. 2—Results of tuberculin tests at ages 5–20 in 21 areas of England and Wales, showing mean percentage positive in South urban, North urban, and rural areas.

The curves representing the percentage of positive reactions rise progressively from the age of 5 years up to that of 20 and show two noteworthy features. The first is that the level is consistently higher for the North urban group than for the South urban. The other is that the levels for the rural group in the early school ages are distinctly higher than those of the urban groups; they remain higher than those for the South urban group throughout, but their curve crosses that for the North urban group at the age of 17–18.

At the age of 5 years, 9·3% of the children tested are positive in South urban areas, 13·5% in North urban areas, and 20·3% in the rural areas—i.e., in the rural areas 1 of every 5 children had had a tuberculous infection before entry to school, compared with 1 of 11 children in the South urban areas. By the age of 14, the final year of school for most children, half the children in the rural areas had been infected, nearly half of those in the North urban areas, and just over 1 in 3 in the South urban areas. There appears to be a distinct rise in adolescence, and at ages 19–20 73·6% are positive in the North urban group, 65·0% in the rural group, and 59·3% in the South urban group.

Though, for reasons given, the analysis is mainly concerned with the total of persons positive in each group, it is interesting to consider, for those persons who were positive, what proportion were positive only to 100 T.U. Each of the figures set out below is the mean of the percentages for areas in the geographical group:

Age-group (years)	*South urban*	*North urban*	*Rural*
5–9	37	34	26
10–14	33	40	28
15–20	24	31	25

The figures are lowest in the rural group—i.e., the degree of positivity was higher there than in the urban

TABLE II—PERCENTAGE POSITIVE* RESULTS OF TUBERCULIN TESTS IN SOUTH URBAN, NORTH URBAN,† AND RURAL AREAS

Area	Age (years)												
	5	6	7	8	9	10	11	12	13	14	15–16	17–18	19–20
Urban England (south of Rugby)..	9·3	10·4	14·2	17·7	21·2	23·6	27·4	31·1	31·9	34·6	40·3	51·0	59·3
Urban England (North and Midlands) and Wales	13·5	13·8	18·3	21·5	25·1	32·7	32·6	38·9	41·7	46·2	55·0	64·1	73·6
Rural England and Wales.. ..	20·3	22·7	26·5	28·2	33·1	38·8	42·4	47·3	47·7	49·4	57·2	61·7	65·0
Total	14·5	15·8	19·9	22·6	26·6	32·1	34·5	38·5	40·9	43·9	51·5	59·6	66·6

* The percentages given are the unweighted averages of the percentages shown by the individual areas within each of the three groups.
† Excluding Calder Valley.

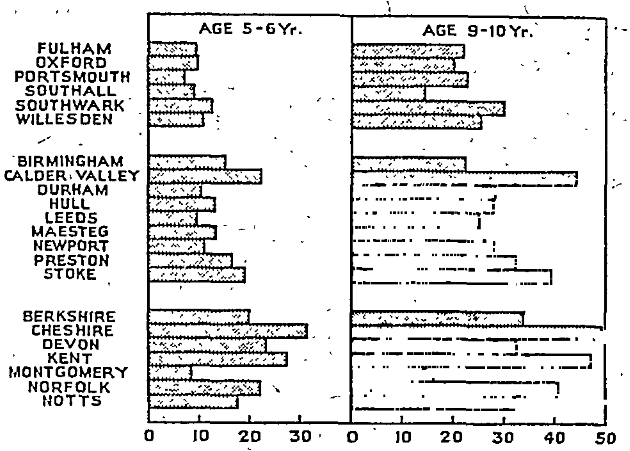

Fig. 3—Percentage tuberculin-positive at ages 5–6 and 9–10 years in 22 areas in England and Wales.

areas. It is also of interest that the figures are lower in the 15–20 age-group than in the children 5–14.

Ustvedt (1948) considers that a reaction of less than 10 mm. diameter to 100 T.U. is non-specific. The standard for the Survey was a reaction (with infiltration) 5 mm. or more in diameter. The proportion of total positives who were *positive only to 100* T.U., *with infiltration* measuring 5–9 mm., was 14% in children aged 5–9 years, 9% in the 10–14 age-group, and 7% in the 15–20 age-group.

RESULTS IN 22 AREAS—ALL PERSONS

The detailed results in each of the 22 areas are set out in table III, and figs. 3 and 4 show graphically the results for two-year age-groups (5–6, 9–10, 13–14, 17–18). The figures show a relatively small scatter of results within the three geographical groupings, and thus add weight to the differences already noted between these groups.

At *ages 5–6*, the proportion positive is under 10% in 4 of the 6 South urban areas, and under 15% in all 6. In the North urban areas it is under 10% only in Leeds, and over 15% in 4 of the 9 areas; in the Calder Valley it is over 20%. In the rural areas it is over 15% in 6 of the 7 areas, and over 20% in 5 of them. The one low figure in the rural areas is for Montgomery, which at this age has the second lowest figure for the 22 areas (the lowest being for Portsmouth); it will be seen that the figures for Montgomery remain exceptionally low throughout. The highest figure is that for rural Cheshire, where 1 of every 3 children entering school at the age of 5 years was positive; this compares with only 1 in 20 in Portsmouth.

At *ages 9–10* similar differences are seen. In the South urban areas 4 of the 6 are under 25% and all are under 30%. In the North urban areas only Birmingham has under 25% positive; 3 of the 9 are over 30%, and in the Calder Valley the figure is over 40%. In the rural areas 6 of the 7 are over 30% (the exception is again Montgomery); 3 are over 40%.

At *ages 13–14* the level is under 40% in all 6 South urban areas, but in only 2 (Birmingham and Durham) of the 9 North urban areas. In the rural areas it is under 40% only in Montgomery.

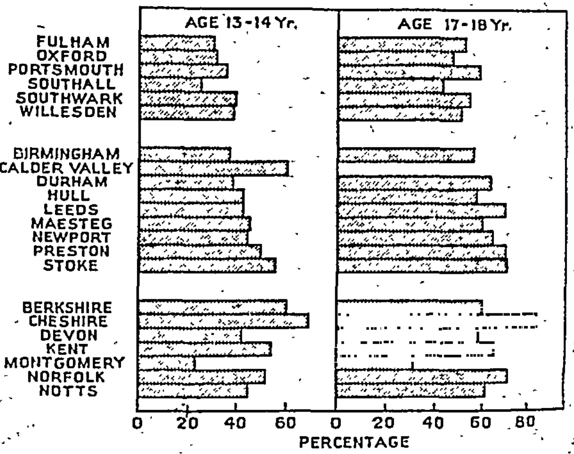

Fig. 4—Percentage tuberculin-positive at ages 13–14 and 17–18 in 22 areas in England and Wales.

At *ages 17–18* the level is under 60% in all South urban areas, in 3 of the 9 North urban areas, and in 2 of the 7 rural areas. By far the lowest figure at this age is for Montgomery, with still only 31% positive; the only 2 other areas with less than 50% positive by this age are Southall with 43% and Oxford with 47%. The highest levels are for 2 rural areas: Cheshire with 85%, and Norfolk with 71% (but the totals for this area are small and at age 19–20 the figure is 65%). The next highest figures are for 3 North urban areas: Leeds, Preston, and Stoke, with just over 70%.

TABLE III—PERCENTAGE POSITIVE RESULTS OF TUBERCULIN TESTS IN 22 AREAS OF ENGLAND AND WALES

Area	Age (years)												
	5	6	7	8	9	10	11	12	13	14	15–16	17–18	19–20
Urban England (south of Rugby):													
Fulham	8·7	10·4	16·0	16·4	20·7	23·5	25·6	27·6	27·1	33·7	38·7	52·6	51·9
Oxford	9·6	9·5	12·0	18·3	17·6	19·1	22·3	27·5	31·0	31·1	41·4	46·8	59·2
Portsmouth ..	5·1	8·7	10·7	15·2	22·1	25·5	27·4	31·2	34·5	35·9	44·5	58·8	67·2
Southall	10·2	8·1	11·9	13·0	13·5	15·3	23·5	23·1	25·4	25·1	31·6	42·7	53·2
Southwark ..	10·7	15·0	17·4	23·3	27·9	32·2	32·8	39·5	37·4	40·7	45·7	54·5	63·6
Willesden	11·2	10·6	17·1	20·3	25·4	26·1	32·8	37·5	36·0	41·3	39·8	50·5	60·7
Urban England (North and Midlands) and Wales:													
Birmingham ..	16·5	14·0	18·2	16·5	21·5	25·3	22·1	36·8	31·8	40·9	46·0	56·2	66·7
Calder Valley ..	21·1	23·8	28·0	34·4	41·9	46·1	46·2	50·0	58·5	61·6	..	..	..
Durham	10·4	11·1	14·6	18·5	25·6	30·9	32·6	32·9	38·0	37·9	51·5	63·9	68·3
Hull	11·8	14·3	18·1	19·0	21·9	32·9	32·9	35·1	40·0	44·0	49·5	57·5	69·9
Leeds	9·8	9·6	19·0	18·9	24·0	26·6	31·9	34·6	38·5	45·9	57·8	70·2	76·4
Maesteg	14·2	12·7	17·6	20·8	21·5	31·7	24·0	40·2	42·2	47·5	61·1	59·7	73·9
Newport (Mon.) ..	9·6	12·5	13·9	23·6	24·7	32·7	32·3	42·8	43·8	44·3	51·5	64·4	80·0
Preston	15·6	17·5	18·9	25·9	27·3	37·1	38·6	42·9	46·6	51·6	63·2	70·4	80·0
Stoke	19·8	18·7	27·1	28·7	34·1	44·3	46·3	46·2	52·5	57·3	59·1	70·7	73·9
Rural England and Wales:													
Berkshire	16·7	22·4	23·1	24·8	29·3	36·8	42·1	49·7	51·1	63·5	58·7	60·2	61·6
Cheshire	30·0	32·6	36·4	37·5	48·1	51·6	65·7	61·7	69·7	67·6	77·4	85·0	82·4
Devon	22·5	24·8	27·3	27·6	28·5	36·4	36·5	35·3	40·6	43·1	52·9	58·3	65·8
Kent	27·4	27·5	39·2	37·9	44·9	49·6	46·9	52·0	55·4	51·4	60·8	64·8	66·9
Montgomery ..	8·4	8·7	12·4	15·9	12·8	19·7	17·4	20·2	21·7	24·6	31·1	31·0	50·0
Norfolk	20·7	23·7	24·8	30·0	36·5	44·6	52·4	49·3	51·3	51·4	67·1	71·2	64·8
Notts	16·3	19·3	22·0	23·4	31·5	33·1	37·7	41·6	44·1	44·1	52·7	61·3	63·2

TABLE IV—PERCENTAGE POSITIVE * RESULTS OF TUBERCULIN TESTS IN MALES AND FEMALES IN SOUTH URBAN, NORTH URBAN,† AND RURAL AREAS

Area	Sex	Age (years)							
		5–6	7–8	9–10	11–12	13–14	15–16	17–18	19–20
Urban England (south of Rugby)	M	9·0	15·7	21·3	30·5	35·6	40·9	54·4	66·3
	F	10·6	16·1	23·6	27·9	31·5	39·9	47·8	55·7
Urban England (North and Midlands) and Wales	M	13·6	20·7	29·2	36·9	44·3	57·2	66·4	73·3
	F	13·7	19·2	28·6	34·9	43·6	53·0	61·1	73·2
Rural England and Wales	M	21·5	28·0	34·9	44·3	48·1	58·8	65·2	68·7
	F	21·7	26·5	37·3	42·4	48·8	54·4	57·8	63·4
Total	M	14·9	21·7	28·8	37·5	43·1	53·1	62·6	69·8
	F	15·5	20·8	30·1	35·4	41·8	49·7	56·2	64·5

* The percentages given are the unweighted averages of the percentages shown by the individual areas within each of the three groups.
† Excluding Calder Valley.

RESULTS IN MALES AND FEMALES

The results are set out separately for males and females in geographical groupings in table IV and fig. 5, and in the 22 areas in table V.

Between the ages of 5 and 10 there is no consistent difference between the two sexes in the percentage positive.

Between the ages of 11 and 14 there are slightly more positive among the boys than the girls. In the 13–14 age-group the difference is greatest in Fulham, Southwark, Willesden, Birmingham, Calder Valley, Leeds, Stoke, and the Kent rural districts; it is least in the rural areas, and is by no means consistently present in the urban communities.

Above the age of 14 the male excess is generally more pronounced and, for all areas combined, at ages 15–16 the male/female ratio is 1·07; at 17–18 it is 1·11; at 19–20 1·08.

RESULTS IN SERVICEMEN

Results for Areas Other than Survey Areas

The results for 3450 men aged 18–20, examined on entry to the Services, and giving a home address other than in one of the Survey areas, are set out in table VI. Urban areas have been divided into "large urban" (towns with over 50,000 inhabitants) and "small urban" (towns with 50,000 or less, but more than 3000).

The same difference as has already been noted appears between the English urban areas of the South and North; the percentage positive is lower in the South urban areas. There is little difference between urban and rural areas.

All types of area being considered, England has the lowest figures, and in England the figures are consistently lowest in the South. Scotland has the highest figures: 75% positive at age 18, compared with 64% in England and 65% in Wales; 77% positive in Scotland at age 19–20, 69% in England, and 72% in Wales.

The figures are, on the whole, slightly higher than those found in the Survey areas; thus, in urban areas of the Midlands and North, the figures for the Services at ages 19–20 are 80% and 77%, against 73% for the Survey areas.

Inclusion of Service Results in Survey Areas

As already stated, where Servicemen gave a home address in one of the Survey areas the results of their tests were added to those for the respective areas, in order to increase the small numbers available in the upper age-groups. At ages 19–27, 209 were added in this way (about 13% of the total). At age 18 the number was 1092, almost half the total.

In view of the fact that the Survey figures were somewhat lower than those obtained for Servicemen in other areas, and also that the Service figures added to the age-group 17–18 were all for men aged 18, it was thought that the inclusion of Service results might have artificially raised the proportion positive for males aged 17–18 in the Survey areas. An analysis made to check this showed that the figure had in fact been raised in this way, but only slightly: thus in South urban areas it was 53·6% for civilians and 54·4% for civilians plus Servicemen; in North urban areas 65·9% and 66·4%; in rural areas 63·3% and 65·2%.

The Servicemen aged 18 can be considered more representative of the populations in their areas than the civilian males aged 18 who volunteered to be examined for the Survey, and it is reassuring that the results are fairly similar.

The levels for males with or without inclusion of Service figures are higher than those found for females, and the findings concerning the difference between males and females are therefore not invalidated.

In the Survey areas the total of females aged 18 was 1171; the total of males, including Service additions, was 2083. It may be considered that, since the proportion positive is higher in males than in females in the 15–20 age-group, the addition of figures for males only may have artificially raised the percentage positive for all persons (tables II and III). However, here again analysis shows that the increase in proportion positive resulting from Service additions was small; in South urban areas from 50·0 to 51·0%; in North urban areas from 62·5 to 64·1%; and in rural areas from 60·1 to 61·7%.

ANNUAL INFECTION-RATES

From the changes in proportion of negative reactors in succeeding age periods it is possible to calculate the proportion of tuberculin-negative children who became

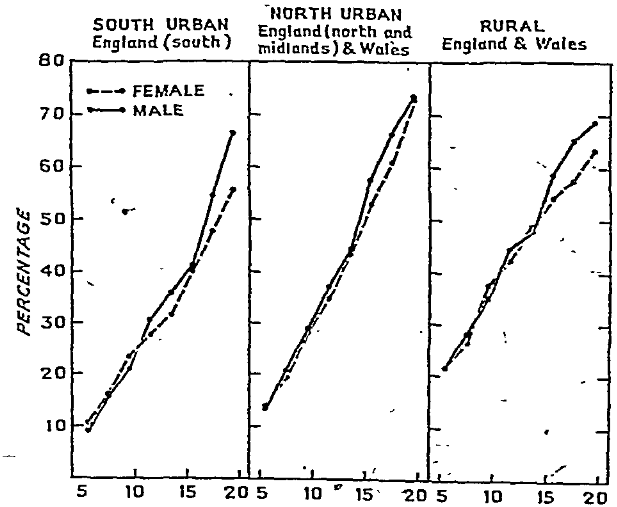

Fig. 5—Mean percentage tuberculin-positive in males and females in South urban, North urban, and rural areas at different ages.

TABLE V—PERCENTAGE POSITIVE RESULTS OF TUBERCULIN TESTS IN MALES AND FEMALES

Area	Sex	Age (years)							
		5–6	7–8	9–10	11–12	13–14	15–16	17–18	1
Urban England (south of Rugby):									
Fulham	M	8·4	15·6	25·7	30·0	37·2	35·4	59·3	66·
	F	10·5	16·6	18·5	24·2	26·1	42·2	50·0	
Oxford	M	6·6	12·3	15·7	26·3	29·9	44·2	51·3	60·
	F	12·9	17·7	20·8	23·3	32·3	38·6	40·5	
Portsmouth	M	7·5	14·6	22·1	28·9	34·9	49·2	63·2	79·
	F	6·6	11·4	25·6	29·1	35·4	39·6	52·6	
Southall	M	6·7	12·2	15·2	21·9	26·0	29·8	49·8	66·
	F	11·2	12·5	13·5	24·6	24·4	33·5	36·1	
Southwark	M	13·9	21·6	26·9	38·6	43·3	47·5	53·1	61·
	F	11·4	19·1	34·1	33·6	36·7	44·8	56·5	
Willesden	M	10·8	17·8	22·2	37·6	42·5	39·1	50·0	63·
	F	11·0	19·6	29·0	32·8	34·1	40·8	51·1	
Urban England (North and Midlands) and Wales:									
Birmingham	M	14·4	19·5	24·9	32·4	40·3	46·8	58·7	70·
	F	16·1	15·3	22·0	26·8	31·8	44·7	51·3	
Calder Valley	M	21·2	30·6	46·3	51·6	63·2	..	..	..
	F	23·7	31·4	41·6	44·3	56·6	..	..	
Durham	M	10·5	15·6	28·5	33·2	38·7	54·9	70·2	70·
	F	11·0	17·3	28·0	32·4	37·2	47·0	45·7	
Hull	M	11·9	19·8	26·8	31·2	42·2	49·3	69·4	68·9
	F	14·4	17·1	29·2	36·7	42·1	49·6	51·4	
Leeds	M	10·5	22·2	24·4	36·2	45·2	59·3	70·1	77·6
	F	8·9	15·4	26·3	30·3	39·1	55·4	70·5	
Maesteg	M	13·9	19·9	27·0	31·4	39·4	58·8	57·4	66·7
	F	12·9	18·5	25·7	31·8	50·7	66·7	64·0	
Newport (Mon.)	M	12·2	18·5	26·7	39·3	42·0	56·8	65·2	83·3
	F	9·6	19·3	29·8	38·1	46·4	44·7	63·0	
Preston	M	16·9	23·5	34·7	42·7	48·6	66·7	68·5	76·1
	F	16·5	21·8	30·2	39·0	49·6	60·8	72·6	
Stoke	M	18·5	26·6	40·8	48·6	57·7	65·0	71·8	73·2
	F	20·0	29·0	38·0	43·8	51·6	55·1	70·0	
Rural England and Wales:									
Berkshire	M	18·8	26·4	32·3	45·9	55·4	58·9	67·6	60·7
	F	21·0	21·2	34·0	45·5	59·9	58·5	55·7	
Cheshire	M	31·6	36·5	47·8	62·5	70·0	80·1	85·6	84·6
	F	31·4	37·4	51·9	64·6	67·4	72·3	83·9	
Devon	M	21·5	27·2	30·2	39·7	41·5	54·4	59·5	66·7
	F	26·0	27·7	35·2	31·5	42·2	51·9	57·1	
Kent	M	29·4	40·8	48·5	49·8	57·2	64·3	67·5	64·3
	F	25·3	36·2	46·3	48·6	47·3	49·2	57·9	
Montgomery	M	10·3	14·7	14·9	18·3	22·2	32·7	34·7	66·7
	F	6·6	13·5	18·1	19·3	24·0	29·9	27·3	
Norfolk	M	23·2	28·2	37·1	52·8	52·1	68·1	75·9	65·5
	F	21·2	20·4	44·0	49·1	50·9	66·7	67·6	
Notts	M	15·5	22·3	33·3	41·2	38·3	53·4	65·8	72·7
	F	20·3	23·0	31·3	38·5	49·6	52·0	54·9	

positive within a year—i.e., the annual infection-rate.* This does not take into account the fact that some tuberculin-positive children may have become negative. Annual infection-rates calculated on this basis are shown for successive 2-year periods, for males and females, in table VII.

It can be seen that there are no obvious changes in rate during the school-age period 5–14, but that subsequently the rate rises considerably in all except the rural female group. The rise in 4 of the 5 other groups takes place between the age-groups 13–14 and 15–16; in the South urban males it appears in the next 2-year period.

It is justifiable, on these findings, to calculate a single infection-rate for the school years, and a second for the subsequent period (it must be emphasised that this applies only to the mean figures for grouped areas). These are shown in table VIII. The annual infection-rates during school age are lower in the South urban areas than in the North urban and rural areas, where the rate is just over 5%. After school-leaving age the infection-rate is more than doubled in all the urban groups; in the rural male group there is a smaller rise; in the rural females it remains virtually unchanged.

RESULTS RELATED TO ENVIRONMENT

Age 5–14—Social Grading

An attempt was made to relate the results of tuberculin tests to the social background. The schools were graded, by the local education officer, in relation to what was known in general of the economic conditions of children's homes. The possibilities of the inquiry in direction were unavoidably very limited, and the re of the analysis were equivocal. In 2 of 4 areas which adequate information was received the propo

TABLE VI—RESULTS OF TUBERCULIN TESTS IN 3450 SERV MEN AGED 18–20 FROM AREAS OTHER THAN THOSE SURVEY

Large urban = towns with over 50,000 population.
Small urban = towns with 50,000 or less but more than 3
Rural = communities with 3000 population or les

Area	Age 18		Age 19–20	
	Total examined	Positive	Total examined	Positiv
Large urban:				
England—				
London	490	293 (60%)	63	44 (70%
South (other)	338	202 (60%)	74	45 (61%
Midlands and North	434	292 (67%)	75	60 (80%
Wales	55	40 (73%)	14	9 (64%
Scotland	151	113 (75%)	33	26 (79%
Small urban:				
England—				
South	429	266 (62%)	87	58 (67%
Midlands and North	465	319 (69%)	73	56 (77%
Wales	61	39 (64%)	18	14 (78%
Scotland	78	60 (77%)	18	15 (83%
Rural:				
England—				
South	211	128 (61%)	51	30 (59%)
Midlands and North	81	56 (69%)	16	11 (69%)
Wales	61	36 (59%)	25	18 (72%)
Scotland	38	27 (71%)	11	7 (64%)
All areas:				
England	2448	1556 (63·6%)	439	304 (69·2%
Wales	177	115 (65·0%)	57	41 (71·9%
Scotland	267	200 (74·9%)	62	48 (77·4%
Total	2892	1871 (64·7%)	558	393 (70·4%

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* The annual infection-rate has been calculated as follows: if N_x is the percentage negative at a given age, and N_{x+t} the percentage negative t years later, and r the annual rate of infection, then

$$N_{x+t} = N_x e^{-rt}.$$

tuberculin-positive was higher in the less economically favoured groups; in 1 it was consistently lower at all ages; and in the 4th there was no difference.

Age 15–20

Grading of the type described above was not possible in respect of young people not at school. At ages 15 and 16, however, there are sufficient figures from most areas to warrant a comparison between young people at school and others already at work. The combined results from 14 areas with reasonable numbers in each category are given in table IX. The unexpected finding is that the proportion positive is slightly higher in the school groups than in the others; the differences, however, are not statistically significant.

Above the age of 16, in most areas, the numbers in school groups are so much smaller than the others that a comparison is not warranted. At the age of 17, in 4 areas for which it was possible to make the comparison (Berks, Kent, Oxford, and Portsmouth), there is no significant difference between results for young people at school and the others.

Discussion and Summary

Despite limitations set by the fact that technique and interpretation of tuberculin tests may vary widely, a survey of the extent of tuberculin sensitisation gives valuable information for tuberculosis control. It is particularly useful in comparisons between different types of community, and between groups of different ages. The survey reported here was the first to cover representative areas of England and Wales. It has given a composite picture of the prevalence of tuberculous infection in this country; over 94,000 children and young people between the ages of 5 and 20 were examined, in 22 areas.

In rural areas of England and Wales the proportion tuberculin-positive rose from 20% at age 5 to 65% at ages 19–20; in urban areas of Southern England from 9 to 59%; and in other urban areas, mainly northern, of England and Wales from 13 to 74%.

TABLE IX—PERCENTAGE TUBERCULIN-POSITIVE AT AGES 15 AND 16. SCHOOLS AND OTHERS. 14 AREAS*

—			Total no. tested	Number tuberculin-positive	Percentage tuberculin-positive
Age 15	Male	Schools	860	434	50·5
		Others	603	294	48·8
	Female	Schools	890	407	45·7
		Others	569	258	45·3
	Persons	Schools	1750	841	48·1
		Others	1172	552	47·1
Age 16	Male	Schools	492	271	55·1
		Others	866	432	49·9
	Female	Schools	383	192	50·1
		Others	810	390	48·1
	Persons	Schools	875	463	52·9
		Others	1676	822	49·0

* Fulham, Oxford, Portsmouth, Southall, Southwark, Willesden; Birmingham, Durham, Preston, Stoke, Berks, Cheshire, Kent and Norfolk.

The difference between North and South urban areas was consistent at all ages from 5 to 20; it must be considered in relation to the fact that the tuberculosis death-rates in urban areas of Wales and Northern England are higher than those for urban areas of Southern England.

The most striking difference found was that between rural and urban areas. The combined figures for rural areas show that at the age of entry to school 1 of every 5 children was already infected; the South urban areas averaged 1 in 10, the North urban areas 1 in 8. Ever since records were available, the prevalence of tuberculosis of human origin, as gauged by death-rates from pulmonary tuberculosis, has been notably less in rural areas than in the towns, and it is therefore probable that the more extensive infection in young country children must be attributed to a bovine rather than a human source. Most of the milk retailed in the large cities is now pasteurised, whereas in the country areas much milk is sold raw, and comes from non-attested

TABLE VII—ANNUAL INFECTION-RATES IN SUCCESSIVE 2-YEAR PERIODS

Area	—	Age (years)														
		5–6		7–8		9–10		11–12		13–14		15–16		17–18		19–20
Males:																
Urban England (south of Rugby)	Percentage negative	91·0		84·3		78·7		69·5		64·4		59·1		45·6		33·7
	Annual infection-rate		3·8		3·4		6·2		3·8		4·3		13·0		15·1	
Urban England (North and Midlands) and Wales	Percentage negative	86·4		79·3		70·8		63·1		55·7		42·8		33·6		26·7
	Annual infection-rate		4·3		5·7		5·8		6·2		13·2		12·1		11·5	
Rural England and Wales ..	Percentage negative	78·5		72·0		65·1		55·7		51·9		41·2		34·8		31·3
	Annual infection-rate		4·3		5·0		7·8		3·5		11·5		8·4		5·3	
Total	Percentage negative	85·1		78·3		71·2		62·5		56·9		46·9		37·4		30·2
	Annual infection-rate		4·2		4·8		6·5		4·7		9·7		13·2		10·7	
Females:																
Urban England (south of Rugby)	Percentage negative	89·4		83·9		76·4		72·1		68·5		60·1		52·2		44·3
	Annual infection-rate		3·2		4·7		2·9		2·6		6·5		7·0		8·2	
Urban England (North and Midlands) and Wales	Percentage negative	86·3		80·8		71·4		65·1		56·4		47·0		38·9		26·8
	Annual infection-rate		3·3		6·2		4·6		7·2		9·1		9·5		18·6	
Rural England and Wales ..	Percentage negative	78·3		73·5		62·7		57·6		51·2		45·6		42·2		36·6
	Annual infection-rate		3·2		7·9		4·2		5·9		5·8		3·9		7·1	
Total	Percentage negative	84·5		79·2		69·9		64·6		58·2		50·3		43·8		35·5
	Annual infection-rate		3·2		6·2		3·9		5·2		7·3		6·9		10·5	

TABLE VIII—ANNUAL INFECTION-RATES IN MALES AND IN FEMALES AT SCHOOL AND IN LATER ADOLESCENCE

Area	—	Males aged					Females aged				
		5–6		13–14		19–20	5–6		13–14		19–20
Urban England (south of Rugby)	Percentage negative	91·0		64·4		33·7	89·4		68·5		44·3
	Annual infection-rate		4·3		10·8			3·3		7·3	
Urban England (North and Midlands) and Wales	Percentage negative	86·4		55·7		26·7	86·3		56·4		26·8
	Annual infection-rate		5·5		12·3			5·3		12·4	
Rural England and Wales ..	Percentage negative	78·5		51·9		31·3	78·3		51·2		36·6
	Annual infection-rate		5·2		8·4			5·3		5·6	
Total	Percentage negative	85·1		56·9		30·2	84·5		58·2		35·5
	Annual infection-rate		5·1		10·4			4·7		8·2	

herds. The greater degree of infection of country children is not confined to the under-5s, but is apparent throughout the school ages. It is interesting to note that, in the survey on non-pulmonary tuberculosis made by the Medical Research Council in England and Wales during the second world war the proportion of bovine-type infections was found to be highest in the 5–9 age-group; reasons were given for believing that this was partly the result of the greater amount of raw milk consumed by children under the milk-in-schools scheme. The present findings support this conclusion.

The sampling was reasonably good in respect of school-children; over the age of 14 it was difficult to arrange tuberculin testing of sufficiently large and representative groups of young people. With this reservation concerning the results in the age-group 15–20, interesting results were revealed by an analysis of annual infection-rates. These were estimated from the changes in percentage of negative reactors in succeeding age-groups. The rate, for all areas combined, varied between 3·2% and 6·5% in the school years; in the age-group 15–20 it was much higher, between 6·9% and 13·2%. There is an interesting difference between males and females: during the school years the rates were about the same for both sexes, but subsequently the increase in infection-rate was greater in males than in females. Tuberculosis morbidity and mortality figures for adolescents are, on the contrary, higher for females than for males; if the Survey figures concerning infection in this age-group are valid, they indicate that the sex difference in reaction to infection during adolescence is even more unfavourable in females than is revealed in morbidity and mortality statistics.

Comparison with the results of the Prophit Survey (Daniels et al. 1948) indicates that the prevalence of infection has declined in the past ten to fifteen years. The figure in the Prophit Survey of 63%, for boys aged 15–16 coming mainly from urban areas, compares with the figures of 40–55% in the present Survey. Similarly at ages 18–19, 80–85% of persons in the Prophit Survey were found to be tuberculin-positive, compared with 59–74% at ages 19–20 in the present Survey. The reduction can reasonably be attributed at least in part to the greater availability of heat-treated milk in the large towns.

Degree of tuberculin sensitivity has not been analysed in detail, because of technical variables which could be responsible for differences between one small group and another. The modified jelly test, used as the first test, proved to be useful for all age-groups tested, and revealed more true positives than did the unmodified jelly test; on the other hand, it could contribute little to measurement of degree of sensitivity, and it is not to be recommended if accurate testing of sensitivity is required for research purposes. As a survey technique it was useful and justifiable.

Persons negative to the jelly test were given a Mantoux test with 100 T.U.; those with reactions of infiltration measuring 5 mm. or more in diameter were counted positive. Small reactions (5–9 mm.) to 100 T.U. are considered by some workers to be in the main non-specific; reactions of this order constituted 14% of all positives in the 5–9 age-group, 9% at 10–14, and 7% at 15–20. An interesting finding was that in children in the rural areas the proportion of positives who were positive only to 100 T.U. was 26–28%, whereas in the urban areas it was 33–40%. Probably where infections originate from milk they are much more frequent than where human infection is responsible—i.e., a country child may be superinfected repeatedly, and maintain thus a high level of sensitivity. Similarly, in the urban areas more frequent infections at 15–20 than at 5–14 may explain the higher degree of positivity that was found in the upper age-groups.

It was not possible to correlate the results of tubercu testing with environment or with the social status the persons tested. There were too many variab It must be emphasised in conclusion that the Surv was a fact-finding investigation, designed to give wit a short time a broad picture of the prevalence of tub culous infection in this country; to elicit other inforr tion would have required techniques more intensive more rigorously standardised than those used.

It would be impossible to name all the people who rende invaluable assistance in organising and carrying out Survey. The nature of the Survey was such that in e area organisation of the work was at least as important the actual execution of the tests, and we are indebted directors of education, their staffs, and the staffs of pub health departments, school-teachers, school nurses, and hea visitors, the staffs of mass-radiography teams, and m others. The doctors directly concerned with the Survey a

Berkshire: Dr. R. T. James, Dr. E. C. H. Huddy.

Birmingham: Dr. J. E. Geddes, Dr. H. M. Cohen, Gordon Evans.

Calder Valley: Dr. G. Wilthew, Dr. B. T. Mann, J. Lyons, Dr. S. Keidan.

Cheshire: Dr. A. Brown, Dr. J. D. Paterson, Dr. A. Len Thorburn.

Devon: Dr. L. Solomon, Dr. L. Meredith Davies, W. J. Doyle.

Durham: Dr. D. M. Calvert, Dr. Ian McCracken, R. W. Locke, Dr. S. Ludkin.

Fulham: Dr. F. A. Nash, Dr. P. L. T. Bennett.

Hull: Dr. L. A. McDowell, Dr. R. Hardy, Dr. Nich Gebbie.

Kent: Dr. G. I. Rees-Jones, Dr. J. M. Morgan, Dr. Elliott.

Leeds: Dr. L. A. McDowell, Dr. F. Ridehalgh, Dr. I. Davies.

Maesteg: Dr. T. Archer Blyton, Dr. N. Tattersall, W. E. Thomas.

Montgomery: Dr. H. E. Seingry, Dr. Ivor J. Jones.

Newport: Dr. T. Archer Blyton, Dr. D. E. Lawrence.

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Notts: Dr. W. Guthrie, Dr. A. C. Tibbits.

Oxford: Dr. R. T. James, Dr. J. F. Warin.

Portsmouth: Dr. J. D. Lendrum, Dr. T. E. Roberts.

Preston: Dr. R. Taylor, Dr. J. S. G. Burnett.

Southall: Dr. W. Pointon Dick.

Southwark: Dr. F. D. Beddard, Dr. E. K. Pritchar Dr. W. Stott.

Stoke: Dr. A. Clark Penman, Dr. V. C. Veitch, Dr. Wotherspoon.

Willesden: Dr. T. Paxon, Dr. D. A. Ashcroft.

Army: Lieut.-Col. A. J. N. Warrack.

Appendix A

DESCRIPTION OF AREAS

The following descriptions have been made as br as possible; they are intended to give only a gene idea of the types of areas covered. In parentheses a given the population (1951 census) of the area survey and the density per square mile. For the urban are *the name of the county precedes the population figur* U.D. = urban district. R.D. = rural district.

Berkshire (31,919; 461).—Area surveyed comprised t borough and R.D. of Newbury. Small market town, su rounded mainly by farming communities, except in t south, where the borough meets the county boundary.

Birmingham (1,112,340; 13,920).—Second largest city England and Wales. Manufacturing centre, with mu heavy industry. Many small industrial undertakings.

Calder Valley, Yorks (57,372; 605).—Group of industri communities (Hebden Royd, Hepton, Ripponden, Sower Bridge, Todmorden) in rural setting. Textile industry.

Cheshire. (whole county: 824,438; 847).—Area compris Nantwich U.D. and R.D. (children) and Northwich (adole cents). Most of the area is rural, but there is mu employment in industries in urban centres.

Devon (43,795; 110).—Area comprised Tiverton and Sou Molton U.D. and R.D. Predominantly farming communitie with many small isolated villages, but including one sma manufacturing centre.

Durham Stanley U.D. (48,123 ; 2474).—Collection of coal-mining villages, with Stanley as business and shopping centre.

Fulham, London (122,047 ; 49,320).—Mainly residential, with some light industry.

Hull, Yorks (299,068 ; 13,233).—City and port with wide variety of industries.

Kent (55,087 ; 330).—The R.D.s of Sevenoaks and Tonbridge. These are partly urbanised and include dormitory areas. The population includes many retired middle-class families.

Leeds, Yorks (504,954 ; 8390).—Large industrial city ; textiles, clothing, engineering.

Maesteg, Glamorgan (23,124 ; 2206).—Coal-mining town near the top of the Llynfi Valley. The U.D. surveyed includes the smaller towns of Nantyffyllon, Caerau, and Llangynwyd (Penybont).

Montgomery (whole county : 45,989 ; 61).—Six representative areas were chosen. Hilly sparsely populated county, with farming and forestry as main occupations, and small light industries in the larger urban areas.

Newport, Monmouth (105,285 ; 8512).—Port with heavy and light industry ; good residential areas.

Norfolk (53,590 ; 182).—The R.D.s of Mitford and Launditch, and Forehoe and Henstead, and the U.D.s of Wymondham and E. Dereham. Mainly farming communities.

Notts (71,528 ; 201).—The R.D.s of Newark, Southwell, and Bingham. Nearly all farming communities. A small urban group from Newark borough was also included.

Oxford (98,675 ; 7500).—University, hospital, and tourist centre, with some heavy industry.

Portsmouth, Hants (233,464 ; 14,976).—Residential, including seaside resort of Southsea, and industrial—ship-repairing (H.M. Dockyard), marine and general engineering.

Preston, Lancs (119,243 ; 13,300).—Industrial (cotton spinning and weaving) and market town and river port.

Southall, Middlesex (55,900 ; 13,728).—Residential and industrial engineering, food production.

Southwark, London (97,191 ; 54,802).—Residential and industrial—engineering, printing, food manufacture.

Stoke, Staffs (275,095 ; 8263).—Highly industrial communities —pottery and coal-mining.

Willesden, Middlesex (179,647 ; 24,805).—Residential and industrial borough in Greater London.

Appendix B

TECHNIQUE OF MODIFIED JELLY TEST

The skin over the interscapular region is cleaned by rubbing firmly with acetone on cotton-wool, and allowed to dry. The skin is then stroked 6 times with a strip of flour-paper 1 in. wide ; the force used should not be so great as to produce visible scratching or erythema. Tuberculin jelly is applied to the skin to form a V with arms about 2 cm. in length. This is covered with a strip of adhesive plaster. The examinee is instructed to remove the plaster after forty-eight hours.

Results are read seventy-two to ninety-six hours after the application of the jelly. An area of raised erythema, with or without vesiculation, at the site of the test constitutes a positive reaction ; there may be coalescence of vesicles to form a V-shaped or heart-shaped area of induration.

(This was the standard for the Survey. In a description published after the end of the Survey Dick (1950) had revised the criteria to read : " Four or more vesicles at the site of application are read as a positive reaction. Less vesiculation . . . is classified as negative.")

It is essential to apply also a control jelly, using flour-paper, until reactions due to over-rubbing (e.g., scoring or abrasion) are readily recognised.

The modified test should not be used in children under 5, for the greater sensitivity of the skin to rubbing makes the test very difficult to read.

REFERENCES

Daniels, M., Ridehalgh, F., Springett, V. H. (1948) Tuberculosis in Young Adults. London.

Deane, E. H. W. (1946) *Lancet*, i, 162.

Dick, W. P. (1950) *Brit. med. J.* ii, 141.

Jonsen, J., Ustvedt, H. J. (1950) *Tubercle*, 31, 261.

Lendrum, J. D. (1951) *Brit. med. J.* ii, 148.

Oppers, V. M. (1951) *Tubercle*, 32, 111.

Palmer, C. E., Petersen, O. S. (1950) *Publ. Hlth Rep., Wash.* 65, 1.

Ustvedt, H. J. (1948) *Int. B.C.G. Congr.* p. 141.

THYMECTOMY IN THE TREATMENT OF MYASTHENIA GRAVIS

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THE purpose of this paper is to report the effect of thymectomy on 100 patients with myasthenia gravis.

Only patients with simple hyperplasia of the thymus are included. Otherwise they form an unselected group, and have been taken in the consecutive order of their names from the thymectomy records of the National Hospital, Queen Square, and New End Hospital, Hampstead. It is not intended to review this group as 100 new patients, for some of them have already been reported by Keynes (1949). The results of surgery, statistically analysed, and those of medical treatment are compared. Almost all of these patients were interviewed and examined by Mr. G. L. Keynes, Dr. E. A. Carmichael, and myself at the same time. The grading of a patient as to A, B, C, &c. (see results) was done at the time and is the unanimous opinion of the three. Most of these patients were referred by the medical staff of the National Hospital, Queen Square.

The value of a survey of this kind depends on several generally limiting features : (1) the natural gross variability, remissions, and exacerbations of myasthenia gravis ; (2) the likelihood of small groups of cases being statistically insignificant ; and (3) the scarcity of cases treated by other means. It is hoped that these difficulties have been overcome.

Study of the literature shows that opinion differs about the value of thymectomy ; unfortunately there are no published reports of a series of cases in which an equal number, selected by random methods, have been treated by either medical or surgical means. The earliest surgical treatment was undertaken by Sauerbruch, but only in recent years have any large numbers been treated by such methods.

Current interest in thymectomy stems from the preliminary report of Blalock (1941), who described the technique and results in 6 patients followed for a very short time. In a second paper Blalock (1944) gave the results in 20 patients who had been followed for a longer but variable time. There were 3 postoperative deaths in this group, and about half the remaining patients were either entirely symptom-free or much improved ; the remainder were either slightly improved or unchanged. It was Blalock's opinion that the procedure was beneficial. He was the first to recognise that the shorter the preoperative duration the better was the chance of improvement after operation—an observation shown to be unequivocally true.

Harvey (1948) reported on 125 patients of whom 32 underwent thymectomy ; 25 of these had a benign hyperplasia of the thymus, the remainder tumours. He has also reported frequency of remissions. Total or partial improvement which persisted for months or years was termed a remission. Of the 125 patients 30 had remissions. 8 patients had a significant remission lasting from three months to two years ; 9 had remissions lasting between two and fifteen years. The results of thymectomy are difficult to evaluate in so small a group as 32. 3 patients died immediately after operation ; of the remainder, 2 were symptom-free, 6 had an almost complete remission of symptoms, 7 had partial improvement, and 5 slight improvement, and in 9 the course of the disease was unchanged ; 7 died later. It is most unlikely that any valid conclusions can be drawn from these diversified results.

TABLE I—THREE GROUPS OF CASES TREATED BY MEDICAL MEANS ALONE COMPARED WITH THE PRESENT SERIES

—	Present series	Kennedy and Moersch (1937) med. treatment only (no neostigmine)	Boothby (1936) med. treatment only	Eaton et al. (1949) med. treatment only
No. of cases ..	100	87	82	173
Group A	41	10 (*11·5*%)	41 (*50·0*%)	?
Group B	26			
Group C	20	—	17 (*20·7*%)	86 (*49·7*%)
Group D	6	28 (*32·2*%)		
Dead from myasthenia	1	24 (*27·6*%)	12 (*14·7*%)	21 (*12·1*%)
Death from other causes	6	10 (*11·5*%)	5 (*6·0*%)	—
Untraced or unknown	0	15 (*17·2*%)	7 (*8·6*%)	?
Length of follow-up (years) ..	4·5	4·5	4·0	2

For the definition of the groups see text.

Viets (1950), reporting on the results of thymectomy in 29 patients with thymic hyperplasia, states that the results *of surgery are not striking.*

Eaton et al. (1949) reported the effect of thymectomy on 32 patients from a total series of 206 cases of myasthenia gravis. Of these 32 patients, 15 were found to have tumour and 17 benign hyperplasia. In an additional 18 the diagnosis of thymic tumour was made by radiography. These latter 18 patients did not undergo thymectomy. The incidence of tumour of 15% is roughly in agreement with Keynes (1949), who found neoplasms in 12%. Of the 15 patients in whom thymoma was found, 1 died on the third post-operative day, 3 were not improved, 4 showed moderate and 7 considerable improvement. Of the 17 who did not have tumours, 3 died within six months of operation, 6 were not improved, 5 showed moderate and 3 considerable improvement. In all, about 60% of those operated on showed some improvement.

On the other hand, Keynes (1949) reports more optimistically on the value of surgery. He has operated on about 150 patients without tumour, and found 65% greatly improved, with a further 30% moderately improved. Keynes believes that the best results are obtained in the youngest patients.

There are reports of three large series of cases that have been treated without surgery.

Kennedy and Moersch (1937) reviewed the history of 87 patients observed from 1915 to 1932, by which date neostigmine had not become available as a remedy. They paid particular attention to the frequency and duration of remissions. 27 patients had 43 complete remissions lasting 1 month to 15 years, averaging 2·2 years; 13 patients had 17 partial remissions lasting from 1 month to 16 years, averaging 1·5 years; and 44 patients had no remissions. The results of treatment with various remedies showed that 34 patients were dead, 24 from myasthenia and 10 from unrelated causes. Of the remaining 53, the state of health of 12 was unknown, 20 were more or less the same, 10 were improved, 8 were worse and 3 were untraced. Harvey (1948) and many others say that remissions are more frequent and last longer in patients who have never received neostigmine.

TABLE II—DISTRIBUTION OF CASES BY AGE

Age at onset (years)	No. of cases	Age at onset (years)	No. of cases
0–9	1	40–49	7
10–19	23	50–59	0
20–29	47	60–69	1
30–39	21		

Boothby (1936) investigated 82 patients who had been treated for six years with neostigmine, ephedrine, and potassium chloride. Of these, 41 were improved to full or half time work and 17 were confined to home or bed. 17 had died—12 from myasthenia gravis—and 7 were untraced.

Another large group of non-operated patients is that of Eaton et al. (1949). Of the 173 patients, 12% were dead within two years of their first visit to the clinic, and 50% had to restrict their work in spite of intensive medical treatment.

These three groups of medically treated patients are presented in tabulated form for comparison with the present series (table I).

PRESENT SERIES

The material presented here consists of 100 consecutive patients with myasthenia gravis who have had benign hyperplastic thymuses removed surgically. Almost all the cases were referred to the surgeon from physicians, and on the whole they were the more severe and rapidly progressive cases. All the surgery was done by Mr. G. L. Keynes by the same technique (Keynes 1949). For the purpose of classifying the results of operation the patients have been divided into four categories after the manner of Keynes (1949).

Group A.—Quite well, no symptoms or treatment.

Group B.—Symptoms inconstant and minor—e.g., only present at menses.

The patient is able to carry on with a full scale of activities with no limitations whatsoever due to myasthenia gravis. Treatment, if any, is irregular and is significantly less than before the operation.

Group C.—Considerable improvement. These patients have fewer or less severe signs and symptoms, and the response to a significantly smaller dose of neostigmine is as good or better than before the operation.

TABLE III—COMPARISON OF AGE AT ONSET AND PREOPERATIVE AND POSTOPERATIVE DURATION OF GROUPS A–D

Group	Mean age at onset (yr.)	S.D.	Mean pre-operative duration (yr.)	S.D.	Mean post operative follow-up (yr.)	S.D.	No. of cases
A	24·9	2·9	2·5	1·8	5·0	2·4	41
B	24·4	7·8	7·0	6·4	3·8	1·9	26
C	27·9	13·1	7·0	6·5	3·7	2·3	20
D	29·0	10·6	7·4	4·3	3·5	3·0	6
C + D	28·2	12·4	7·0	6·3	3·6	2·4	26

S.D. = Standard deviation calculated by the method of Brownlee (1949).

Group D.—Unchanged or worse.

A final group comprises those patients who have died since operation from either myasthenia or some other cause.

DISCUSSION

Of the 100 patients 73 were female and 27 male. The mean age of onset was 31 years and the range of ages is given in table II.

Table III and its statistical verification in table IV show that the age of onset of the disease in this series makes no difference to the ultimate result of operation. What is important, however, is the interval between the onset of the disease and the operation. In the patients who benefited least from the operation (groups C

TABLE IV—STATISTICAL VERIFICATION OF DIFFERENCES OF MEANS OF AGE AT ONSET, PREOPERATIVE DURATION, AND POSTOPERATIVE FOLLOW-UP BETWEEN GROUPS A–D

Comparison of	Between groups	t.	Degrees of freedom	Result
Age at onset	A + B	0·37	65	Insignificant
	A + (C + D)	1·6	65	„
	B + (C + D)	1·2	50	„
Preoperative duration	A + B	4·2	65	Highly signif. (to 0·001)
	A + (C + D)	4·4	65	„ „ „
	B + (C + D)	1·3	50	Insignificant
Postoperative follow-up	A + B	1·9	65	„

and D) the myasthenia had lasted longest. The length of follow-up of all four groups is the same.

Table III also shows that the total period of observation of patients in group A is 7·5 years, whereas those in groups B, C, and D have been under observation for about 11 years. Though the postoperative duration of all groups is the same, it might reasonably be said that, if group A were observed for the same length of time as the other groups, some of group A might become B, C, or D. However, 22 of the patients that Keynes (1949) reported as A are included in group A here, and none of the remainder of his A patients have become B, C, or D. If the greater duration of the B, C, and D groups were significant, surely some of the A patients of Keynes's report would have become B, C, or D in the two and a half years between his report and the present one. This is not so.

TABLE V—NUMBER OF TABLETS OF NEOSTIGMINE DAILY BEFORE AND AFTER OPERATION (1 TABLET = 15 MG.)

Group	Mean preoperative dose (tablets)	S.D.	Mean postoperative dose (tablets)	S.D.
A	12·1	2·9	0	—
B	12·7	8·9	6·8	4·8
C	23·2	42·9	10·0	6·8
D	*	—	—	—

* The number of D cases being only 6, and the treatment so variable, it is impossible to give a mean that really represents an average dose or imparts any real information.

From tables V and VI the details of the preoperative and postoperative treatment may be seen. As the size of dose of neostigmine taken is a rough guide to the severity of the myasthenia, it is obvious that preoperatively groups A and B were therapeutically the same, while group C was much more severe. Further evidence of the benefit of operation to groups B and C is the significant decrease in the amount of neostigmine given postoperatively. One may state then, that the proportion of patients with myasthenia gravis that are either entirely relieved of symptoms and all treatment or can make a significant reduction in the amount of treatment with clinical improvement after operation in this series is 87% (A + B + C).

Table I, which compares three other groups of cases treated with medicine only, shows that none of the other three has as high a percentage of A and B cases. It is equally obvious that the bigger death-rates are in the medically treated cases.

Remissions.—Each patient included in this series was questioned about remissions. A remission for this purpose was defined as a period of a month or longer during which the patient needed no treatment or a substantially reduced treatment while continuing or increasing his activities. In group A, 3 patients had 5 remissions. 2 patients experienced 1 remission each, lasting four months and one year. The 3rd patient had 3 remission lasting four years, two and a half years, and nine months. When operated on, he had been in an exacerbation for eighteen months. In group B there were no remissions, and in group C there was one remission lasting six months.

Deaths.—Of the 7 patients who have died postoperatively only 1 died of myasthenia gravis. She was aged 41 and died at home six weeks after the operation; she had been discharged from hospital much improved and was reducing her neostigmine daily. Of the remaining 6 patients, 1 man, aged 40, died of abdominal carcinomatosis seven years after operation, his myasthenia gravis having been completely relieved in the interval. A woman, aged 30, died of pulmonary œdema, cause unknown, six years after operation; her interval result was A. In the remaining 3 cases the cause of death is unknown. The state of the myasthenia gravis was classified as A in 2 cases and B in 1.

TABLE VI—STATISTICAL VERIFICATION OF DIFFERENCES OF MEANS IN PREOPERATIVE AND POSTOPERATIVE TREATMENT BETWEEN GROUPS A–D

Comparison of treatment of	t.	Degrees of freedom	Result
B before and after operation	4·8	50	Significant (to 0·001)
A and B preoperatively	0·24	65	Insignificant
C before and after operation	6·6	38	Significant (to 0·001)

SUMMARY

Of 100 patients with myasthenia gravis who had benign thymomas removed surgically 87 show complete relief of symptoms, considerable or moderate improvement, or improvement as judged by the reduction in daily neostigmine requirements after operation. The average period of follow-up was four and a half years after operation.

The benefit from surgery was greatest in the patients who had had myasthenia for the shortest time before operation. In this series the age of onset is not significant.

Comparison with three large series of patients treated by medical means alone reveals that among these the proportion of cured or greatly improved is smaller, and the proportion of deaths due to myasthenia gravis much higher, than in the group presented here.

I wish to thank Mr. G. L. Keynes for allowing me to see these cases and present this study; to Dr. E. A. Carmichael for seeing some of the patients, for supervision of the survey, and for advice and criticism on the paper; to the staff of the National Hospital, Queen Square, for permission to use their cases; the Medical Committee for permission to publish this information; and Miss M. A. Crosskey, of the neurological research unit of the Medical Research Council, for advice and assistance with the statistical analysis.

REFERENCES

Blalock, A. (1941) *Amer. J. Surg.* 54, 149.
— (1944) *J. thorac. Surg.* 13, 316.
Boothby, W. M. (1936) *Trans. Ass. Amer. Phys.* 51, 188.
Brownlee, K. A. (1949) Industrial Experimentation. London: H.M.S.O.
Eaton, L. M., Clagett, O. T., Good, C. A., McDonald, J. R. (1949) *Arch. Neurol. Psychiat.* 61, 467.
Harvey, A. M. (1948) *Bull. N.Y. Acad. Med.* 24, 505.
Kennedy, F. S., Moersch, F. P. (1937) *Canad. med. Ass. J.* 37, 216.
Keynes, G. (1949) *Brit. med. J.* ii, 611.
Viets, H. R. (1950) *Ibid*, i, 139.

A REVIEW OF
TWO HUNDRED CHRONIC ALCOHOLICS

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IT is unhappily true that the great body of lay and medical opinion regards alcoholism—compulsive drinking—as a hopeless disease determined by moral failure. This has led to an apathy on the part of all authority, confusion of thought and practice, and a too ready acceptance of results that are undeniably poor. Thus the recovery-rate of alcoholism remains very low; an atmosphere of pessimism envelops the patient, his relatives, and his doctor; and a stigma of recidivism attaches to all sufferers. The advertised poor prognosis and the usual environment of treatment may prevent the alcoholic from seeking help, and in all these ways the community may be robbed of valuable or even outstanding members.

It should be significant that no one form of therapy, or combination of forms, claims a satisfactory recovery-rate when tried on any considerable number of alcoholics, and that nearly all forms of treatment show an over-all recovery-rate of only about half the number treated. It would seem, therefore, that the secret of therapy lies not so much in its nature as in its application to each individual case.

This paper reviews the 200 alcoholics I have treated personally and followed up for one to five years. Far less than half of this group of men and women have recovered from their disability. That is the over-all picture, but scrutiny reveals that alcoholics cannot be considered in the mass. Before any kind of treatment is even considered they must be assorted by psychiatric methods, according to the personality before the onset of excessive drinking.

Thus four drunken men will have the common factor of intoxication and addiction to alcohol, but their response to treatment may be quite different. Prognosis depends on psychiatric evaluation of personality, and recovery depends on their insight into their problem, and their desire to recover. Usually they can be placed in one of four categories :

1. Alcoholics of good previous personality.
2. Alcoholics with an underlying neurosis.
3. Alcoholics with an underlying psychosis.
4. Alcoholics of psychopathic personality.

ASSORTMENT OF PATIENTS

At the first or after a few interviews I classify my patients according to their replies to a questionnaire designed to show the previous personality.

The questionnaire begins with an investigation of the drinking history of the patient and his desire for recovery. This is followed by an exploration of his childhood experiences, his sexual history and development, and his marital status. At a further session I ask him questions about his religious attitude, his affiliations, his occupation, and his hobbies. The answers to parts of the questionnaire, especially those dealing with the patient's sex life, are often more easily and truthfully obtained under thiopentone narcosis. The whole questionnaire is designed to discover every possible way in which alcohol plays a part in the patient's modus vivendi. To deal with obvious points, the early age at which drunkenness begins may be a pointer to schizophrenia ; the reasons for drunkenness may reveal inadequacies of personality—inferiority, aggression, sexual tension, or even true psychosis. The social integration of the patient may be judged by his answers as to his marital status and adjustment, the nature and stability of his employment, and how well he has succeeded in his work.

The most important factor is to establish the genuine sincerity of the patient. Frank admission of his inability to control his drinking is an essential step towards his recovery. If he is able to understand his problem, he is also able to grasp the necessity for total and permanent abstinence.

For the first group, simple rest and a vitamin-fortified diet will restore physique. Superficial psychotherapy, together with "specific" treatment of his alcoholism, should hold out the highest hope of his recovery to permanent sobriety.

The second group, of alcoholics with an underlying neurosis, will require a much longer course of psychotherapy. The choice of psychotherapist again is important—he must be a warmly human person.

For the third group the diagnosis of an underlying psychosis calls for its treatment in a suitable environment and not for the treatment of the superadded alcoholism.

But if the survey reveals a member of the fourth group —a psychopathic personality—responsibility and sincerity cannot be looked for. Gillespie (1934) offers a useful definition of the psychopathic personality as having an apparent lack of moral and social sense, an inability to learn from experience, and capacity for being a social nuisance. The problem here is not one of the treatment of alcoholism, and no method of cure can be measured against it. The alcoholism is but one aspect of a defective character make-up and it is well-nigh hopeless to attempt to treat it. Perhaps it is even wrong, for these inevitable failures lower the recovery-rate of all methods of treatment and brings them into disrepute. In considering compulsive drinkers we should therefore regard these moral defectives as a separate problem. Responsibility for them is not yet in the hands of medicine, but somewhere else in the social scheme, and certainly not in themselves. They present a medicolegal challenge.

ÆTIOLOGY

The 200 men and women investigated in this paper have been drawn almost entirely from the higher educational or social levels. The men have reached at least fair professional eminence, or have inherited means and responsibility. The women have been the wives of such men, or of respectable attainment in their own right. Thus their defection through alcoholism has almost always been a loss to the community and the need for their recovery is correspondingly strong.

The outlook is best for middle-aged patients, for people of 35 to 55 years of age are free from the irresponsibility and unawareness of youth as well as from senescence and indifference of age.

The 200 patients were assorted thus :

Of previous good personality	83
With underlying neurosis	25
Of psychopathic personality	76

The remaining 16 had such severe general, neurological, or psychotic disorder that their alcoholism did not call for specific consideration.

If complete sincerity, full insight, and entire responsibility are the touchstone for real treatment and good prognosis, it will be seen that less than half of these alcoholics merit assessment.

TREATMENT

Treatment for all patients has followed a general pattern, and I make no special claim for any one method employed. As soon as possible after admission, treatment directed to breaking down the alcoholic pattern is begun (Williams 1950) along the lines recommended by Dent (1941) in this country, and by Voegtlin (1940) in America. Dent uses apomorphine as a nauseant and emetic, and gives it in varying doses every few hours for several days, either orally or parenterally. He does not claim that apomorphine acts by producing a conditioned-reflex aversion, but it seems to remove the desire for alcohol. Voegtlin uses the nauseant emetine to elicit the unconditioned reflex of nausea and vomiting. The sight, smell, and taste of alcoholic drinks serve as the conditioning stimulus and thus a conditioned reflex is established, creating a distaste for and definite aversion to alcohol.

Emetine is given by mouth and by hypodermic injection, together with pilocarpine and ephedrine. Pilocarpine is thought to combat the physical taste for liquor, and ephedrine is used to combat the fall in blood-pressure experienced by some patients after emetine administration. I explain frankly to the patient the details of treatment, the action of the drugs, and the reason for their administration, and at every point I invite his coöperation.

An important decision, which must be reached after several treatments, is when to end the course. I base this decision on the degree of aversion which has been established and the patient's general mental attitude. The proper degree of aversion is reached when the sight or smell of alcohol produces nausea, and the proper mental attitude when the patient declares that he no longer desires alcohol in any form and wants to have nothing to do with it again. It is difficult to recognise these two points without long experience of the technique.

The successful use of 'Antabus' depends once more on the integrity of the patient, for he must not fail to take regularly the prescribed dose. It serves as a reminder to the patient who, while admitting his problem, has not finally accepted his need for complete abstinence from every form of alcohol.

Thus, treatment is calculated to induce an aversion to alcohol. Yet many workers have found that patients who have never developed a true or lasting aversion have maintained sobriety. The conditioned reflex is not the whole answer, although an unsatisfactory response to the effects of nauseant drugs often foretell a poor result. The physical debilitation brought about by emetine and apomorphine seems to be accompanied by a profound disruption of other aspects of the patient's personality and a total change in outlook. A phase of increased suggestibility follows, during which the patient is particularly amenable to simple and forceful psychotherapy stressing his need for permanent sobriety and his ability to achieve and maintain it. He must accept that for a compulsive drinker, moderate drinking is an impossibility. An acknowledged slip may be of good prognostic value, since it reinforces the patient's realisation of the absolute need for total abstinence.

Treatment is often followed by an astonishing repair of faculty and loss of tension; a new lucidity of thought and interest, and acceptance of ideas and responsibilities. Many workers (Sargant 1949, Gottesfeld and Yager 1950) find that for the neurotic the physical approach facilitates psychotherapy which before was unacceptable and tedious.

Inpatient treatment takes a maximum of three to four weeks. After "specific" treatment the time is used to allow the sympathetic attitude of the staff, the effect of patients upon each other, and discussion of common problems to consolidate recovery, and to consider practical measures for rehabilitating the patient in his profession and with his friends.

RESULTS

Alcoholics with Good Previous Personality

Of the 83 patients with good personality, 75 (90%) remained sober for six months, of whom 48 (58%) have remained sober for one to four years; 27 (32%) from six months to just under a year. 6 relapsed under six months and I have no information about 2 patients. 3 of the 48 relapsed after two years' sobriety but presented themselves for further treatment; 10 of the 27 maintained sobriety for over six months but relapsed under one year. By "relapse" I mean return to alcoholism, and not one mild "slip" which is acknowledged and remitted.

Alcoholics with Neurotic Personality

The 25 patients with an underlying neurosis were given general and specific treatment, and in some cases a prolonged course of psychotherapy. 14 (56%) of these patients were sober after six months, 6 (24%) of whom have remained sober for more than one year. 11 relapsed under six months.

Alcoholics with Psychopathic Personality

Of the 76 patients of psychopathic personality, 2 (2·6%) remained sober for two years after which they both relapsed; 2 remained sober for six months only. The remaining 72 all relapsed under six months, usually within weeks of discharge. Some were drug addicts as well or have since so become.

DISCUSSION

All this shows how difficult it is to accept any over-all figures of recovery or relapse with any method of treatment, and how misleading and discouraging the picture given by such figures may be to the alcoholic who most earnestly desires to seek treatment and who most surely would benefit by it.

But if it is accepted that a satisfactory rate of recovery can be reached for fundamentally normal men or women, the treatment of alcoholism becomes a hopeful project. Surely these are the people who are bound to suffer most from our present methods of assessing alcoholics in the mass. The less satisfactory recovery-rate obtained among neurotic drinkers does but underline that for their own sakes the neurotics must receive treatment different in type and duration from the better adjusted alcoholics, lest comparison deepen their neurosis.

The almost hopeless prognosis for the psychopathic personality addicted to alcohol distorts the figures of recovery, just as the high incidence of psychopathy among alcoholics unfairly saps the public trust in the recovered alcoholic of good personality.

FOLLOW-UP AND GROUP THERAPY

From the first it became obvious that the scepticism of intelligent and well-educated men and women could be confounded and their resolution fortified by meeting with fellow alcoholics at all stages of treatment and recovery. So the newly admitted patient is encouraged to mix with his fellows in an atmosphere of complete frankness of discussion and of friendly concern for each other's affairs. This has helped to disperse harmful reserve and a sense of shame. On their routine or sporadic visits, recovered alcoholics usually like to see and talk to those under treatment, in a friendly spirit of display and sympathy. This need or wish to keep in touch with one another can further be met by sociotherapeutic groups, such as our dining-club which meets regularly to discuss, round the after-dinner table, the problems of the alcoholic (Williams 1951). Some of these patients have been introduced to the Alcoholics Anonymous movement which has enabled them to help other alcoholics with benefit to themselves. The partnership between doctors and Alcoholics Anonymous is proving useful and is one which should be encouraged.

At present the patient is so unlikely to find his own and his doctor's belief in the reality and durability of his recovery shared by his world, so liable to be received with wariness and distrust, that one cannot withhold admiration from the many recovered alcoholics whose resolution has remained undismayed over the years. They are the strongest proof that fundamentally normal people can recover from alcoholism and of the value of the material recovered.

SUMMARY

The present over-all recovery-rate from alcoholism is low for all forms of treatment, being less than half of the total number treated. But analysis of any considerable number of patients shows that for certain groups the outlook is far better than this suggests.

Alcoholics can be broadly assorted into those of good previous personality, those with an underlying neurosis, those with a psychosis, and those of psychopathic personality. The recovery-rate varies widely between these four groups.

Recognition of these facts should further the cause of the fundamentally normal alcoholic and stimulate medical interest in his problem.

I am greatly indebted to Dr. W. L. Voegtlin, the physicians and technicians of the Shadel Sanitarium, Seattle, U.S.A., for their great courtesy and kindness, for access to their patients, their questionnaire and demonstration of the conditioned-reflex therapy.

REFERENCES

Dent, J. Y. (1941) Anxiety and its Treatment. London.
Gillespie, R. D. (1934) *Proc. R. Soc. Med.* 27, 1147.
Gottesfeld, B. H., Yager, H. L. (1950) *Quart. J. Studies on Alcohol*, 11, 222.
Sargant, W. (1949) *Proc. R. Soc. Med.* 42, 3.
Voegtlin, W. L. (1940) *Amer. J. med. Sci.* 199, 802.
Williams, L. (1950) *Brit. J. Addict.* 47, 2.
— (1951) The Sober Truth. Leicester.

ASSAY OF A.C.T.H. ON THE THYMUS OF THE NESTLING RAT

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METHODS of assaying adrenocorticotrophic hormone (A.C.T.H.) have been investigated for many years, but for a long time the lack of demand for the material meant that there was little impetus behind the work. Three years ago the picture changed completely when the dramatic effect of the hormone on rheumatic diseases was demonstrated, and when the urgent demand for large-scale preparation emphasised the lack of an easy and accurate method of assay. Since that time many attempts have been made to evolve such a method, but reliance is still placed mainly on the difficult Sayers test (Sayers et al. 1948).

Several reviews of methods of assaying A.C.T.H. (e.g., Reiss et al. 1951) have recently appeared[*]; all that need be said here is that methods fall broadly into two groups, those based on acute and those based on chronic effects of A.C.T.H. The former include tests based on discharge of cortical steroids, depletion of adrenal cholesterol or of ascorbic acid, and changes in blood characteristics, &c., which occur within an hour or two of the intravenous administration of A.C.T.H.; the other tests include those based on maintenance or restoration of adrenal size or morphology, changes in thymus weight, &c.

For tests of the first group it is essential to use hypophysectomised animals, since in the presence of the pituitary gland comparatively slight stress or shock causes a brief outpouring of endogenous A.C.T.H., which gives rise to acute changes similar to those caused by exogenous A.C.T.H. For some of the other tests hypophysectomised animals are less essential, because the threshold for the response is much higher and the occasional slight stress caused by handling and injection does not produce the continuous strong stimulus necessary for a chronic effect.

The use of hypophysectomised animals is inevitably a complication; and, in considering possible methods of routine assay for bulk preparations, the chronic high-threshold reactions seemed to offer certain advantages. In particular we turned our attention to the reaction of the rat's thymus, which decreases greatly in size under the influence of cortical steroids (Selye 1950), of A.C.T.H. in the presence of the adrenals (Crede and Moon 1943), and of severe stress in the presence of the adrenals and the anterior pituitary body (Selye 1936, Robertson 1949). The threshold requirement of cortical steroids for this effect is high, and comparatively large doses of the hormones are necessary to produce unequivocal results. Moreover, the effect is essentially chronic and takes some days to appear fully, even in response to a heavy stimulus. The same applies to the response even to severe stress.

These facts, taken in conjunction with Jailer's (1950) report that the stress mechanism is ill-developed in the young rat before the eighth day of life, suggested that the thymus of the nestling rat might have special advantages as a test organ for the assay of A.C.T.H. Moon's (1940) results accorded with this idea, but no serious attention seemed to have been given to the elaboration of an assay method based on this criterion.

The first problem that beset us was the comparative inefficiency of the present rapidly absorbed preparations of A.C.T.H. in producing chronic results when given by once-daily injections. The suspension of the active material in arachis oil containing 5% beeswax (Bruce and Parkes 1952) solved this problem, and the following results were obtained:

(1) Complete hypotrophy of the thymus of the nestling rat could be caused by three daily doses of A.C.T.H. suspended in 5% beeswax in arachis oil. Less than three daily doses were relatively inefficient, and more than three were inconvenient and were unnecessary with reasonable dosage.

(2) There was little delay in the appearance of the maximal response to medium doses of the size suitable for assay; hence the rats could appropriately be killed twenty-four hours after the last injection.

On the basis of these findings an assay method was evolved which is described in detail in the appendix, and of which the chief variables are examined in the body of this paper.

RESULTS

Specificity of Response

It has already been pointed out that a test based on changes which require a continuous stimulus and a high threshold concentration of A.T.C.H. are less likely to be complicated by stress effects than are tests based on acute changes with a low threshold. Nevertheless, extensive control experiments with other hormones and non-specific substances were made.

The following preparations in three daily doses of the amount stated were found to be without demonstrable effect on the size of the thymus of the nestling rat (weighing 10–20 g.) under the conditions of test: acid saline solution 0·05 and 1·0 ml.; protamine zinc insulin 0·25 unit in 0·05 ml. suspending fluid diluted with saline solution; Merck's aqueous vehicle for cortisone 0·1 ml.; arachis oil 0·05 and 0·1 ml.; 5% beeswax in arachis oil 0·1 ml.; rabbit serum 0·1 ml.; œstradiol propionate 1 mg. in 0·1 ml. of arachis oil; progesterone 1 mg. in 0·1 ml. of arachis oil; serum gonadotrophin 100 units in 0·3 ml. of saline solution; and testosterone 1 mg. in 0·1 ml. of arachis oil.

More detailed attention was given to posterior-lobe principles, which often contaminate A.C.T.H. preparations and have complicated other attempts to use intact animals for assay of A.C.T.H. According to our information a bad preparation of A.C.T.H. may contain as much as 100 m.u. of posterior-lobe activity per mg., and a good one not more than 10 m.u. per mg. The heaviest contamination we know of in the preparations used by us in the nestling rats was about 50 m.u. per mg., three daily doses of this amount being the maximum they could have received. Nestling rats, in groups of nine littermates, were therefore given three daily doses of 10 m.u. or 100 m.u. of posterior-lobe extract in 0·1 ml. of wax-oil by the usual test method. Average thymus weights at the end of the test were respectively 217 and 219 mg. per 100 g. of body-weight in comparison with that of 221 for the untreated controls. It is therefore extremely unlikely that A.C.T.H. assays carried out by the technique described here are complicated by posterior-lobe effects.

A further experiment was made in which two groups of rats were handled four times a day for three days to give twelve injections of 0·05 ml. saline, or 0·005 mg. of adrenaline in 0·05 ml. saline. Neither treatment caused a significant decrease in thymus weight compared with untreated controls, though the figure for the adrenaline-treated rats was the lowest. It may be concluded that mild stress, even if repeated several times a day, does not demonstrably affect thymus weight under the conditions of this test.

The only definite positive result produced with non-specific substances was obtained with formalin, which, as Selye showed long ago, is a severe stressing substance.

At all ages tested (0, 1, 2, 3, 4, 5, 6, 7, 8, and 19 days) the thymuses of rats injected with 0·01 ml. of 5% formalin per g. of body-weight daily for three days were smaller than those of the controls. The differences from normal, which varied from 10 to 40%, were rather greater in animals in which injections were started at the ages of 5, 6, or 7 days, but there was no doubt about the effects in the younger rats. Results obtained on larger rats after adrenalectomy by us and other workers suggest that the effects of formalin on the thymus are mediated entirely by the response of the adrenals to stress, and it therefore seems that Jailer's (1950) conclusions about the time of appearance of the stress mechanism in the young rat are not of general application. It should be emphasised that the dose used by us, though not as large as that used by Selye, was nevertheless highly toxic. The resulting effects on the thymus were such as would be produced by a comparatively small dose of A.C.T.H. (0·1–0·4 I.U.).

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[*] Dr. Li and his associates (Reinhardt, W. O., Geschwind, I. I., Li, C. H. *Acta endocrinol.* 1951, 8, 393) have recently emphasised the importance of rate of absorption in the biological assay of A.C.T.H., and the need for caution in drawing conclusions from the apparent comparative activities of different preparations assayed by different methods.

This matter has been discussed at some length because the possibility of non-specific effects is a critical one when entire animals are used for the assay of A.C.T.H. So far as the thymus-weight criterion of A.C.T.H. activity is concerned, it may be concluded that, although very severe stress will affect the thymus of the young rat at any age in the same way as will a small dose of A.C.T.H., there is no evidence whatever that the very mild stress associated with the A.C.T.H. assay on the thymus of such rats produces any complications. It seems justifiable, therefore, not only to use intact young rats for assays by the method described but also to use them at a much later stage than might have been anticipated from Jailer's results.

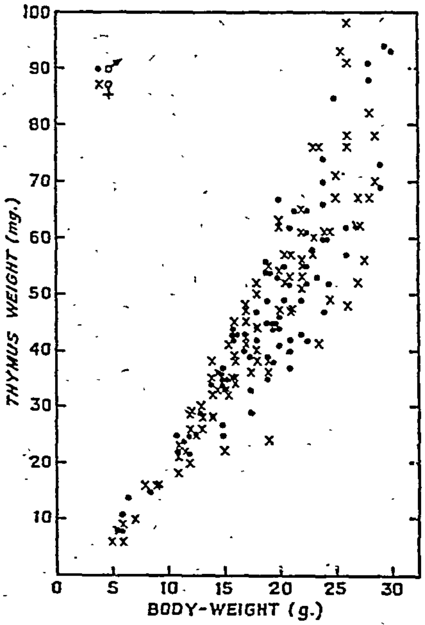

Fig. 1—Relation between body-weight and thymus weight in nestling rat.

Effect of Body-weight on Response and Use of Litter-mates

The thymus of the normal young rat weighs 200–300 mg. per 100 g. of body-weight. Thus at a body-weight of 15 g., at the age of about 10 days, the thymus weighs about 35 mg. (fig. 1). Correlation with age is much less good, and there is no apparent difference between the sexes, at any rate in the nestling rat. Nestling rats grow rapidly, there being roughly a 40% increase in their body-weight (14–20 g.) even during the relatively short period of the assay (three days). Moreover, A.C.T.H. has a well-marked effect in reducing the rate at which the animals grow (table I): those receiving three daily doses of A.C.T.H. 1·6 mg. gain only 10% in body-weight during that period, as opposed to the normal figure of 40%. For these reasons it is not practicable to base the dose for individual rats upon their individual body-weights; not only would this entail individual doses for each rats but also each rat would require a different dose on each day of the test. We have therefore always given the same dose to all the rats in a treatment group, independent of the individual body-weights.

TABLE I—THE EFFECT OF A.C.T.H. ON BODY-WEIGHT DURING THE THREE-DAY TEST PERIOD

(16 litter-mates per group)

Daily dose of laboratory standard preparation of A.C.T.H. (mg.)	Average initial weight (g.)	Average final weight (g.)	Percentage increase in weight in three days
None	14·8	20·1	42
0·4	15·1	18·5	23
0·8	14·9	16·8	13
1·6	15·4	16·9	10

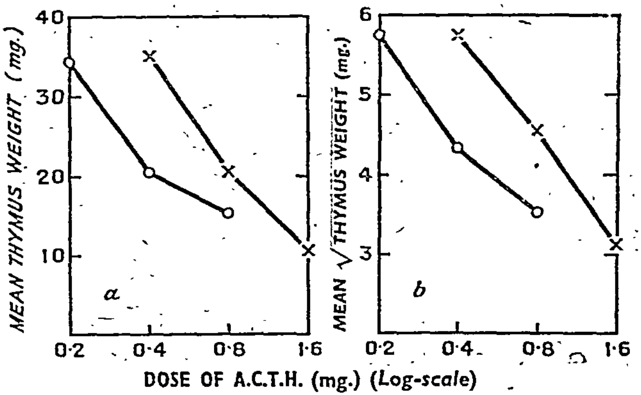

Fig. 2—Dosage response lines of an assay: a, before transformation; b, after transformation; x, laboratory standard preparation of A.C.T.H.; o, test batch A_1.

To reduce the variation between the different treatment groups, we have in all our tests used litter-mates, distributing at random one member of each litter to each treatment group. It will be seen later (table III) how much this procedure aids in reducing the error variance of the test. Nevertheless, even within single litters there is sometimes considerable variation in the body-weights of individual rats, and it was necessary to find out to what degree the response—i.e., the final thymus weight—was influenced by the rat's initial body-weight. Three daily doses of 0·4 mg. of a batch of A.C.T.H. reduced the thymus weight of rats weighing about 12 g. by nearly two-thirds, but the comparable reduction in rats weighing about 19 g. was only about a third; and differences in body-weight of this order may occur within a litter, although litters with such large differences in weight would not normally be used. This effect is so large, therefore, that it was considered essential to equalise the total weight of the rats within each treatment group by appropriate exchange of litter-mates after the original random selection, and this has been done in all our assays.

TABLE II—TYPICAL ANALYSIS OF VARIANCE OF DOSAGE-RESPONSE RELATIONSHIP FOR THE LABORATORY STANDARD PREPARATION USING √THYMUS WEIGHT AND LOG. DOSE A.C.T.H. AS VARIATES

Source of variation	Sum of squares	Degrees of freedom	Mean square	Variance ratio	P
Between doses	53·02	4	13·26	17·38	$< 0·001$
Linearity	46·92	1	46·92	61·53	$< 0·001$
Departures from linearity	6·10	3	2·03	2·67	$> 0·05$
Between litters ..	46·04	10	4·60	6·04	$< 0·001$
Dose/litter interaction..	28·98	38*	0·76	1·00	..
Total	128·04	52	..	..	..

* Two degrees of freedom dropped from the error because 2 missing readings were fitted. These two animals died during the test.

Dosage-response Relationship

To provide a suitable assay method for routine use, it is highly desirable that the dosage-response relationship used should be a linear one. In early experiments we investigated the relation between the logarithm of the dose of A.C.T.H. and various functions of the response, in order to test the assumption of linearity. We used as a laboratory standard a batch of A.C.T.H. (Z.3) prepared by Dr. M. Reiss. It soon appeared that the relation between the logarithm of the dose and the final thymus weight was curvilinear; moreover, there was evidence that the variance of the responses at individual dose levels was significantly correlated to the dose, in such a way that the smaller the mean thymus weight the smaller was the variance of the group. This is undesirable,

TABLE III—RESULTS OF (3 + 3) DOSE ASSAYS COMPARING VARIOUS BATCHES OF A.C.T.H. WITH THE LABORATORY STANDARD PREPARATION OF A.C.T.H.

Test batch	No. of litters	Potency	Slope b	Error variance s^2	$\lambda = \frac{s}{b}$	Variance between litters	V(M)	Weight $\left(W = \frac{1}{V(M)}\right)$	Weight per litter	Percentage limits of error (P = 0·05)
A_1	12	0·550	−3·9	0·83	0·234	4·77	0·0031	321	27	77–129
B	7	0·931	−2·5	0·76	0·348	3·51	0·0115	87	12	60–166
C	10	0·378	−1·4	0·53	0·520	3·91	0·0331	30	3	43–233
A_2	11	0·708	−4·8	1·46	0·252	1·34	0·0042	240	22	74–135
D	4	0·744	−5·0	1·27	0·226	1·24	0·0089	112	28	63–159

since it implies a bias in the accuracy of the test and is contrary to one of the fundamental assumptions for a valid assay (Jerne and Wood 1949). It seemed likely that a square-root transformation of the response would not only tend to be linearly related to the logarithm of the dose but would also tend to eliminate the correlation between dose and variance of response; and consequently we next used this function. Fig. 2 shows the results of one assay. It will be seen that transformation seems to improve both the linearity and the parallelism of the two lines.

TABLE IV—LIMITS OF ERROR EXPECTED FROM A (3 + 3) DOSE ASSAY WITH DIFFERENT NUMBERS OF LITTERS

(Estimated potency is assumed to be unity in all cases)

No. of litters	Total weight $\left(W = \frac{1}{V(M)}\right)$	No. of degrees of freedom	Expected percentage limits of error (P = 0·05)
5	100	20	62–162
10	200	45	72–139
15	300	70	77–130
20	400	95	80–125
50	1000	245	87–115

Analysis of variance of a further experiment, in which five doses of the laboratory standard were administered to litter-mates from eleven litters, is shown in table II. The doses of standard used increased from 0·24 to 1·2 mg. by successive increments of 50%.

It therefore appeared that this relationship could, for practical purposes, be regarded as linear, at least over the dosage range investigated. At the lower dose levels there is an obvious tendency for the dosage-response curve to flatten as the wholly ineffective dose is approached; and there is equally obviously a limit beyond which the thymus weight cannot be further reduced —i.e., when only fibrous connective tissue remains.

We have also tried to improve the dosage-response relationship by doing an analysis with covariance for the initial body-weights, but this did not at all change the general pattern. This may, of course, be due to the care with which the total body-weight in each treatment group was balanced; and, if this step is omitted, analysis of covariance of this sort might well increase the accuracy of an assay, although in our experiments it did not do so.

Design of Routine Assays

It was decided that, in the early stages, assays of the (3 + 3) dose design should be used to test further the assumption of linearity both for the laboratory standard and for the various test preparations investigated. The results of the first five assays of this type are listed in table III. In all the assays the common regression was highly significant ($P < 0{\cdot}001$), there was *no significant* curvature, and the two separate regression lines could be regarded as parallel. It will be seen that the error variance ranged from 0·5 to 1·5 and the slope from 1·5 to 5·0, giving values of $\lambda = \frac{s}{b}$ varying from 0·2 to 0·5 approximately. The limits of error of the assays, however, do not follow the values of λ very closely, and this is due to the enormous difference made by the choice of the dose levels of the test substances. Where the doses of test substance approximated in their effect to the doses of standard, so that the estimate of potency, unadjusted for the actual doses given, approximated to unity, the limits of error obtained were reasonably close. On the other hand, when the potency was less than 0·5 or more than 2·0, the limits of error were very wide in spite of relatively small values for λ. It is thus very important in using this test to give roughly equipotent doses of standard and test preparations, even if this entails a trial run to decide on the dose levels. Where the dose levels were correctly chosen, the limits of error were 75–135% when twelve litters of six rats were used, and 60–150% when about six litters of six rats were used. In other words, the average weight per litter is about 20. From this figure the expected limits of error for assays using different numbers of litters can be calculated, and some of these are shown in table IV.

TABLE V—CALCULATION OF THE RESULTS FROM A TYPICAL ASSAY $\sqrt{\text{THYMUS WEIGHT}}$ (MG.)

Litter no.	Laboratory standard preparation (daily dose)			Test batch A_2 (daily dose)			
	0·4 mg.	0·8 mg.	1·6 mg.	0·2 mg.	0·4 mg.	0·8 mg.	Total
1	6·16	6·56	3·16	8·19	7·28	3·32	34·67
2	7·68	4·69	3·87	6·16	8·37	5·39	36·16
3	8·06	4·58	4·69	8·25	4·36	8·00	37·94
4	5·66	5·48	2·83	6·71	6·40	3·61	30·69
5	6·63	6·56	3·87	5·29	6·00	7·07	35·42
6	7·68	5·66	4·00	8·66	5·57	5·00	36·57
7	6·63	7·28	3·74	7·42	5·00	3·46	33·53
8	7·81	6·56	3·16	7·35	3·46	3·87	32·21
9	7·62	4·24	2·45	5·83	6·32	3·61	30·07
10	5·66	3·61	3·00	6·00	7·55	3·46	29·28
11	6·00	5·10	2·65	7·62	7·48	5·10	33·95
Total	75·59	60·32	37·42	77·48	67·79	51·89	370·49

ANALYSIS OF VARIANCE

—	Sum of squares	D.f.	Mean square	Variance ratio	P
Between substances	8·60	1	8·60*	5·89	< ·05
Between doses	93·85	2	46·92	..	..
Linearity	92·39	1	92·39†	63·25	< ·001
Combined curvature ..	1·45	1	1·45	<1	..
Substance/dose interaction	3·61	2	1·81	..	..
Departures from parallelism	3·60	1	3·60	2·46	> ·10
Opposed curvature ..	·02	1	·01	<1	..
Between litters	13·37	10	1·34	<1	..
Residual (error)	73·03	50	1·46‡	..	..
Total	192·46	65	..	..	..

* D^2 † B^2 ‡ s^2

POTENCY—LIMITS OF ERROR

$D^2 = 8{\cdot}60$ $B^2 = 92{\cdot}39$ $s^2 = 1{\cdot}46$

$k = \sqrt{\frac{8}{3}}$ $I = \log. 2 = {\cdot}30103$

$M = \frac{kID}{B} = \bar{1}{\cdot}84999$ Antilog. $M = {\cdot}70793$

Potency $= 2({\cdot}70793) = 1{\cdot}42$

$s_M = \frac{skI\sqrt{B^2 + D^2}}{B^2} = {\cdot}064623$

$t(5\%$ level, 50 d.f.$) = 2{\cdot}01$. The degrees of freedom are those associated with s^2

Log. limits of error: $M \pm ts_M = \bar{1}{\cdot}84999 \pm {\cdot}12989$

i.e., $\bar{1}{\cdot}72010$ to $\bar{1}{\cdot}97988$

Limits of error: ·52493 to ·95471 or 74·1 to 134·9%

The analyses of these assays also indicated that the between-litter variance averaged about four times the error variance; hence omission to use litter-mates may be expected seriously to reduce the accuracy of the assay.

More recently we have made six assays by the (2 + 2) dose design. These have also been satisfactory except when the dose levels chosen for standard and test were not about equipotent. The values of λ were very similar, again ranging from 0·2 to 0·5 approximately. In the best of the six assays, limits of error of 67–150% were obtained with eight litters of four rats—i.e., an average of 20 per litter—in other words, a litter of four may provide as much information as a litter of six. We have not as yet sufficient evidence to judge whether or not this is likely to be a consistent finding.

SUMMARY

The decrease in weight of the thymus of the intact nestling rat caused by administration of A.C.T.H. has been used as the basis of an assay method.

Neither the mild stresses caused by the performance of the test nor other relevant hormones (except cortisone) cause any demonstrable change in thymus weight under similar conditions. The test is therefore regarded as adequately specific in spite of the use of intact animals.

Variables associated with the test are considered. Full details of the procedure chosen are given in the appendix.

It seems likely that the method provides a comparatively simple quantitative assay of A.C.T.H.

The main disadvantage of the test is lack of sensitivity, making comparatively large amounts of active material necessary.

For the batch of A.C.T.H. (Z.3) which we used as our laboratory standard we are indebted to Dr. Max Reiss, of the Bristol Mental Hospitals, who supplied it as a contribution to a standard preparation of A.C.T.H.

Appendix

ASSAY PROCEDURE

Animals

Young rats aged 7–11 days and weighing 12–20 g. are used. The mother is removed from the cage before the young are handled, and not returned until they are back in the nest. The individuals are identified within the litters, twenty-four hours before the first injection, with small tattoo marks made in the ears with a triangular surgical needle dipped in indian ink. Comparison must be strictly between litter-mates, doses being allotted as described in the test. For speed of dosing, necessary to prevent settling out of the suspension or cooling of the beeswax during the operation, the young are sorted into dosage groups, each group being kept in a container with a warm lining and a cover to prevent the rats from crawling about. Failure to keep the young warm may lead to neglect by the female of the particular individuals and to their consequent loss. Litters are identified with a colour mark to facilitate the return of the correct litter to the mother. The young are weighed at the start of the test, after forty-eight hours, and when the animal is killed. Failure to make the normal weight increment after two days is a useful preliminary indication that an effective dose of A.C.T.H. is being given.

Use of Wax-oil Medium

The wax-oil medium is prepared by dissolving 5 g. of white beeswax in 95 g. arachis oil warmed to about 70°C. It can be used either (1) warm, or (2) at room-temperature.

(1) The A.C.T.H. powder is suspended in the required amount of warmed medium by grinding vigorously with a small part of it and then with the whole in a boiling-tube cut down and roughened inside at the bottom, and fitted with a ground-glass rod. The suspension is rewarmed and stirred vigorously before each injection. This method was used for all the experiments recorded here.

(2) The wax-oil medium, semi-solid at room-temperature, is reduced by vigorous shaking to the consistence of a thick cream, which does not solidify again without reheating, and in which the A.C.T.H. powder can be incorporated and injected at room-temperature. Vigorous grinding is required to make the suspension, which must be stirred thoroughly before each injection. This method gives results similar to those obtained by method (1) above and is more convenient for routine assays.

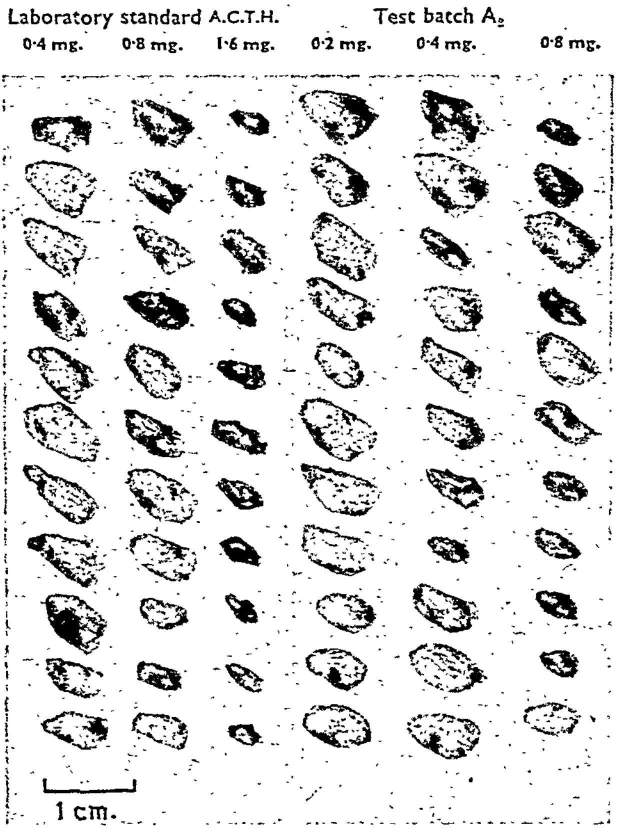

Fig. 3—Thymus glands of all nestling rats used in one assay—i.e., after three days' treatment with A.C.T.H.

Results on protracted heating at 100°C suggest that A.C.T.H. is comparatively stable in the wax-oil medium, but as a routine precaution suspensions are not kept more than a week.

Injections

A wide-bore needle (no. 20 × 1 in.) is necessary to avoid blockage by the particles of A.C.T.H. Three once-daily injections are given, each at a different site. The volume of each injection is usually 0·1 ml. The needle is inserted as far as possible under the skin so that the dose is deposited well away from the skin puncture. The skin is held firmly as the needle is withdrawn and for a few seconds afterwards to prevent the dose from oozing through the hole. Local reactions are rarely produced in rats weighing more than 10 g. with the material in oil or wax-oil.

Dissection of Thymus

The rats are killed with chloroform twenty-four hours after the last injection. The thymus is dissected out and weighed fresh. If necessary, the bodies can be stored at +2°C for up to three days without demonstrably altering the weight of the thymus. Because of the personal element in the dissection of an organ like the thymus, if the work requires two dissectors, each should take whole litters and preferably half of each group. A typical dissection of all the thymus glands used in one assay is illustrated in fig. 3.

Calculation of Results

Table V shows the data from a specimen assay, and the methods used in calculating the result.

REFERENCES

Bruce, H. M., Parkes, A. S. (1952) *Lancet*, i, 71.
Crede, R. H., Moon, H. D. (1943) *Proc. Soc. exp. Biol., N.Y.* 43, 44.
Jailer, J. W. (1950) *Endocrinology*, 46, 420.
Jerne, N. K., Wood, E. C. (1949) *Biometrics*, 5, 273.
Moon, H. D. (1940) *Proc. Soc. exp. Biol., N.Y.* 43, 42.
Reiss, M., Halkerston, I. D. K., Badrick, F. E., Halkerston, J. M. M. (1951) *Analyst*, 76, 461.
Robertson, J. S. (1949) *J. Path. Bact.* 61, 619.
Sayers, M. A., Sayers, G., Woodbury, L. A. (1948) *Endocrinology*, 42, 379.
Selye, H. (1936) *Brit. J. exp. Path.* 17, 234.
— (1950) The Physiology and Pathology of Exposure to Stress. Montreal.

PREVENTION OF ACUTE DINITRO-ORTHO-CRESOL (D.N.O.C.) POISONING

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Dinitro-*ortho*-cresol (D.N.O.C.) is a cumulative poison in man and is eliminated from the body remarkably slowly (Harvey et al. 1951). In Great Britain acute poisoning has occurred in men engaged in the manufacture of D.N.O.C., and in spray operators using D.N.O.C. for the control of weeds in cereal crops (Bidstrup and Payne 1951). No cases of poisoning have been recorded among men who use D.N.O.C. as a late winter wash on fruit trees. Acute D.N.O.C. poisoning has affected most often men spraying cereal crops, and 8 fatal cases have been recorded since 1945.

Measures to reduce the incidence of poisoning among men using D.N.O.C. as a selective weed-killer in cereal crops have included the use of protective clothing and enclosed tractor cabins to reduce the risk of absorption of the material, the instruction of operators in spraying methods and in the recognition of the early symptoms and signs of poisoning, and routine medical examinations. These methods have not proved entirely successful, partly because of the difficulty in diagnosis of D.N.O.C. poisoning in the early stages. If the nature of the illness is recognised and treatment on general lines adopted immediately, recovery can take place even in seriously ill patients (Pollard and Filbee 1951), but death may take place within a few hours of the onset of symptoms, and no specific antidote to D.N.O.C. is yet known (Steer 1951).

Experiments on volunteers showed that, when the blood-D.N.O.C. level was about 20 µg. per g. of blood a further dose of about 1 mg. per kg. led to a sharp rise in the concentration of D.N.O.C. in the blood (fig. 1), and when this was more than 40 µg. per g., all the volunteers had headache, lassitude, and general malaise (Harvey et al. 1951). When the blood-D.N.O.C. level was about 20 µg., all the volunteers experienced an exaggerated feeling of well-being. The significance of this subjective symptom was not appreciated at the time of the experiments; but Mr. F. Hardy, the head of a firm of contract sprayers, directed our attention to its importance as the earliest manifestation of the absorption of D.N.O.C. in significant amounts. He stated that when he observed this "fitter than usual" condition in an employee spraying D.N.O.C., he transferred the man immediately to other work—a practice usually resented because the man felt so well.

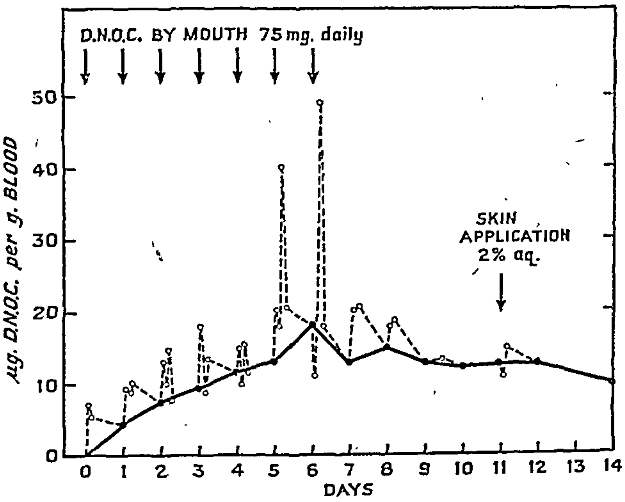

Fig. 1—Effect of absorption of 75 mg. of D.N.O.C. when the blood-D.N.O.C. level is about 20 µg. per g. *Symptoms were present at peak levels.* Note that false high values can be shown if blood-D.N.O.C. level is estimated less than eight hours after last exposure.

The results of the experiments on the volunteers suggested that it would be possible to remove a man from further exposure to D.N.O.C., before toxic symptoms developed, by estimating the blood-D.N.O.C. level at short intervals. To show that the correlation between the blood-D.N.O.C. level and the symptoms existed in the conditions of work in the factory and the field, single estimations were made on blood collected from 23 process workers engaged in the manufacture of D.N.O.C., 39 men using D.N.O.C. as a late winter wash on fruit trees, and 133 spray operators applying D.N.O.C. to cereal crops. The results of these investigations are recorded in tables I and II. Estimations were made by the method described by Parker (1949) on whole blood collected into a tube containing an anticoagulant. Harvey (1952) describes a method for the estimation of D.N.O.C. in 0·1 ml. of blood. Investigations indicate that there is no true correlation between the urinary excretion of D.N.O.C. and the blood-D.N.O.C. level, particularly when the latter is about 20 µg. per g. of blood.

TABLE I—BLOOD-D.N.O.C. LEVELS

—	No. examined	Blood-D.N.O.C. level (µg. per g.)		
		Below 10	10–20	Above 20
Process workers ..	23	22	1	—
Winter-wash sprayers	39	39	—	—
Cereal-crop sprayers ..	133	88	20	25*

* Includes one man who sprayed potato haulm.

The process workers had been employed in the manufacture of D.N.O.C. from six weeks to five years. Many of them showed deep yellow staining of the skin and hair. One man, interviewed in 1948 and observed at that time to have bright yellow hands, face, and hair, had a blood-D.N.O.C. level of only 7·3 µg. per g. of blood, although he had worked continuously on the manufacture of D.N.O.C. for five years. This observation lends support to the view that, although D.N.O.C. is absorbed through the skin, relatively small quantities gain entrance to the body by this route. The fact that only 1 of 23 process workers examined had a blood-D.N.O.C. above 10 µg. (15·7 µg.) per g. illustrates that it is easier to apply and supervise protective measures in the factory than in the field. The low blood-D.N.O.C. in fruit-tree sprayers was anticipated. These men use a much weaker solution of D.N.O.C. than do the cereal-crop sprayers, and the method of spraying produces larger droplets which are less likely to be absorbed through the respiratory tract. 8 men in this group had been spraying D.N.O.C. for more than fifty days.

In the group of cereal-crop sprayers examined no definite correlation was found between acreage sprayed and blood-D.N.O.C. level. The spraying season lasts about six weeks in the late spring and early summer. The habits of each workman, the variable conditions of weather, and the type of spraying equipment are among the many factors which could affect the absorption of D.N.O.C. by men doing this job. It is obvious that the risk of absorbing dangerous amounts of D.N.O.C. is greatest among cereal-crop sprayers. In addition to the fatal cases and cases of acute poisoning which have been recorded in previous years, 45 of 133 cereal-crop sprayers examined in 1951 had a blood-D.N.O.C. level higher than 10 µg. per g., and in 25 of these the level was above 20 µg. per g. There were 4 cases of acute poisoning, 1 of which proved fatal (Steer 1951). The highest blood-D.N.O.C. levels recorded in these 4 cases of poisoning are shown in table II. In case B the blood-D.N.O.C. level was estimated at short intervals until the patient had fully recovered. The results have been reported by Pollard and Filbee (1951). Fig. 2 illustrates the correlation between the blood-D.N.O.C. and the symptoms and signs of poisoning, and the slow rate of elimination of D.N.O.C. from the body. Even when the blood-D.N.O.C. level had fallen from 60 µg. per g. to about 14 µg. per g. on the twelfth day, the basal metabolic rate was still 180.

In our opinion the estimation of blood-D.N.O.C. levels in workmen at risk of absorbing dangerous amounts of this substance would prove a valuable additional measure in the prevention of acute D.N.O.C. poisoning. This should be done at least at weekly intervals, and the man should not return to work with D.N.O.C. until the results are known. If the blood-D.N.O.C. level in blood taken eight hours after the last exposure to D.N.O.C. is 20 µg. per g. or above, the workman should be removed from further contact with this substance for at least six weeks. Since he will have no symptoms unless the blood-D.N.O.C. level is about 40 µg. per g., he can continue with work which involves no risk of absorbing further amounts of D.N.O.C. In cases where the blood-D.N.O.C. level is 10–20 µg. per g. strict supervision is necessary to ensure that the man observes all the recommendations for the safe handling of D.N.O.C. The blood-D.N.O.C. level should be determined again after two days; and, if it has risen higher, the man should be removed from further contact with D.N.O.C. When the blood-D.N.O.C. is lower than 10 µg. per g., no extra precautions are necessary. False high and peak values may be observed if blood is collected less than eight hours after the last exposure to D.N.O.C.

TABLE II—BLOOD-D.N.O.C. LEVELS IN CEREAL-CROP SPRAYERS

Blood-D.N.O.C. level (µg. per g.)	No. of workmen
10–	20
20–	16
30–	5
40– 75–(Case A) Fatal 60–(Case B) Seriously ill 55–(Case C) Seriously ill 44–(Case D) Moderately ill	4

The routine estimation of the blood-D.N.O.C. is intended to augment, and not to replace, the preventive measures described by Hunter (1950) and the recommendations of the Zuckerman Working Party on toxic chemical substances used in agriculture (*British Medical Journal* 1951). Experience in the use of D.N.O.C. in Great Britain shows that men using D.N.O.C. as a selective weed-killer on cereal crops are most likely to develop acute poisoning, although the recently adopted use of D.N.O.C. to destroy potato haulm has also led to a case of acute poisoning (table II, case C). In our opinion inhalation of spray droplets and fine dust which forms on the machine during spraying in hot still weather constitutes the main route of absorption, and we believe that respirators should be worn by all members of the spray crews, and by supervisors or other persons who come into the vicinity of spray operations.

SUMMARY AND CONCLUSIONS

The value of the routine estimation of blood-D.N.O.C. levels in persons at risk of absorbing dangerous amounts in the spraying of cereal crops, the destruction of potato haulm, and the *manufacture of* D.N.O.C. is discussed.

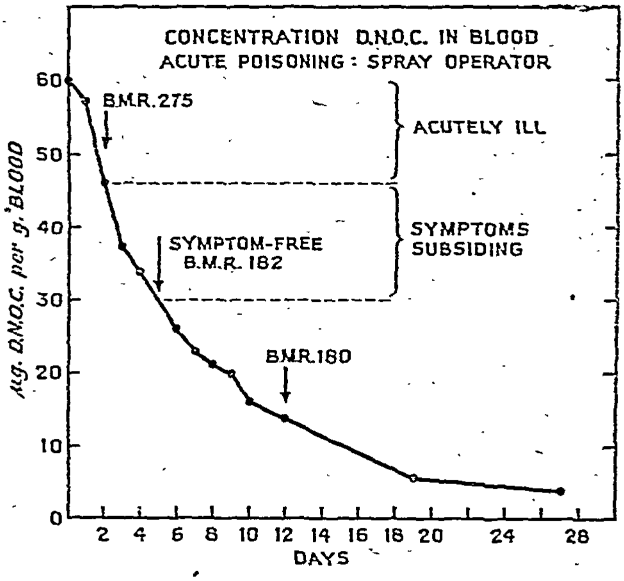

Fig. 2—Correlation of symptoms with blood-D.N.O.C. level (case of Pollard and Filbee 1951).

Single estimations of the blood-D.N.O.C. levels in 133 men engaged in spraying cereal crops, 23 process workers, and 39 fruit-tree sprayers are reported. The estimations were made on samples of whole blood by the method described by Parker (1949).

The blood-D.N.O.C. levels in 4 cases of acute poisoning which occurred in Great Britain in 1951 are recorded and show the correlation between the blood-D.N.O.C. level and the symptoms and signs of poisoning.

It is recommended that a man should be removed from further contact with D.N.O.C. for at least six weeks if the blood-D.N.O.C. level eight hours after the last exposure is 20 µg. per g. or higher.

The main route of absorption is by inhalation, and it is recommended that respirators should be worn, especially by spray operators and others concerned in the spraying of cereal crops.

Harvey (1952) describes a method for the estimation of D.N.O.C. in 0·1 ml. of blood.

Investigations on the correlation between the blood-D.N.O.C. level and the urinary excretion of D.N.O.C. indicate that determination of D.N.O.C. in the urine is unlikely to prove a reliable test of the absorption of D.N.O.C. when the blood-D.N.O.C. level is about 20 µg. per g.

These observations on the relationship between physiological effects and the blood-D.N.O.C. levels in man have developed from impressions based on descriptions of the clinical picture in fatal cases of D.N.O.C. poisoning and have been confirmed by experiments on volunteers and by subsequent examination of men engaged in the manufacture and use of D.N.O.C. Every member of the Department for Research in Industrial Medicine of the Medical Research Council has contributed in some way to the investigations. We are particularly indebted to Dr. Donald Hunter for advice and criticism, and to the management and personnel in factories and spray contracting firms who have coöperated with us in making available the samples of blood.

REFERENCES

Bidstrup, P. L., Payne, D. J. H. (1951) *Brit. med. J.* ii, 16.
British Medical Journal (1951) i, 639.
Harvey, D. G. (1952) *Lancet*, i, 796.
— Bidstrup, P. L., Bonnell, J. A. L. (1951) *Brit. med. J.* ii, 13.
Hunter (1950) *Ibid.* i, 449.
Parker, V. H. (1949) *Analyst*, 74, 646.
Pollard, A. B., Filbee, J. F. (1951) *Lancet*, ii, 618.
Steer, C. (1951) *Ibid.* i, 1419.

ESTIMATION OF DINITRO-ORTHO-CRESOL IN BLOOD

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THE best method for the routine analysis of dinitro-*ortho*-cresol (D.N.O.C.) in blood or urine is that devised by Parker (1949). This method combines simplicity with speed and accuracy and can be carried out with relatively inexpensive and simple chemicals and equipment, most of which are available in clinical laboratories. None of the chemicals requires special purification, except D.N.O.C.; this should be recrystallised twice from aqueous ethyl alcohol before it is used for the preparation of standard solutions. A further advantage of Parker's method is that it can be used to estimate dinitro-*secondary*-butyl phenol (D.N.B.P.), and experiments suggest that solutions containing gram-molecular equivalents of the two substances give colour of approximately equal tint and intensity. No attempt has been made to differentiate D.N.O.C. from D.N.B.P. in the blood of spray operators, and both substances can be estimated as D.N.O.C. The modification of Parker's method described here enables the estimation of D.N.O.C. to be made accurately on 0·1 g. blood. This means that sufficient blood can be obtained by finger-tip or ear-lobe puncture and obviates the need for repeated venepuncture for routine blood-D.N.O.C. estimations.

APPARATUS AND METHOD

The apparatus used in our laboratories is essentially that described by King (1946) with minor modifications. The following items of equipment are required: a stabilised light source from a 6-volt bulb, an iris diaphragm to control the light beam, a dark-violet or dark-blue filter, and a 0·9 ml. cuvette of approximately 25 × 20 × 8 mm., which is held firmly in a 'Bakelite' holder (fig. 1). The transmitted light falls into a selenium photo-electric cell which is attached to a sensitive moving-coil galvanometer. The items can be lined up on a wooden holder; and the analysis is carried out in a dark room, which saves the necessity of encasing the equipment with a more complicated holder. All the essential equipment is readily obtainable.

The light source should be constant; a 3-watt 6-volt lamp worked from a main of accumulator is suitable. An ordinary microscope lamp is adequate. The iris diaphragm controls the quantity of light, and the movable shutter is required to prevent damage to the selenium photo-cell when the cuvette is removed. The cell should have a capacity of less than 1 ml. and is specially constructed so that the long axis is maximal.

The blood should be collected not less than eight hours after the last exposure to D.N.O.C. to avoid false high and "peak" values (Bidstrup et al. 1952). The finger, thumb, or lobe of the ear should be thoroughly cleansed with spirit and punctured with a sterilised needle; a Hagedorn no. 3 is suitable. The blood is allowed to drop directly into a small weighed glass tube, of capacity 5–10 ml., containing a known amount of some anticoagulant such as oxalate or heparin. The tube should be strong enough to stand centrifuging and should be fitted with a ground-glass stopper. It is unnecessary to add any preservative as it has been found that blood-D.N.O.C. concentrations remain relatively constant for at least a week at normal temperatures when kept in well-stoppered tubes.

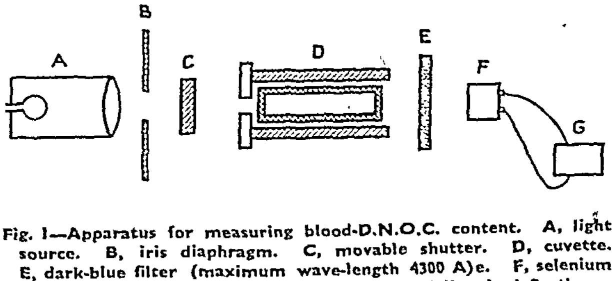

Fig. 1—Apparatus for measuring blood-D.N.O.C. content. A, light source. B, iris diaphragm. C, movable shutter. D, cuvette. E, dark-blue filter (maximum wave-length 4300 A)e. F, selenium photo-cell. G, sensitive mirror-galvanometer (full-scale deflection = 1 micro-amp.). A, D, E, and F are rigidly mounted on a wooden platform.

The stopper is removed and the tube re-weighed. Any traces of blood which adhere to the top, sides, or lips of the *tube are washed down with a small square* (about 1 sq. cm.) of filter-paper dipped in 1% saline. The filter-paper is then added to the blood, followed by 2 ml. of methyl ethyl ketone and excess salt mixture (Parker 1949). The whole is well shaken and centrifuged for five minutes. The ketone is then poured into the absorptiometer cuvette. It is essential to remember that the ketone should always be in excess of the aqueous phase, and if possible this ratio should be at least 2 : 1. The addition of filter-paper squares and small quantities of saline will make no difference to the estimation.

No rapid semi-quantitative techniques have yet been devised for the analysis of D.N.O.C. in blood without the use of suitable photo-electric absorptiometers. It is anticipated that D.N.O.C. concentrations in the blood will be less than 20 µg. per g. in most instances. These will give alkaline colours in the ketone extractive which will be too faint for measurement either by comparison with suitable standards in visual colorimeters or by the naked eye.

Most photo-electric absorptiometers which are fitted with suitable filter systems or else with a diffraction grating will measure with accuracy concentrations of D.N.O.C. in the range 5–20 µg. per g. in 0·5 g. or more of blood, using 5 ml. of methyl ethyl ketone. When 5 ml. of ketone is used for similar concentrations of D.N.O.C. in 0·1 g. of blood there is 95% light transmission, which greatly reduces the accuracy of the method. It is therefore essential to increase the intensity of the colour to be measured. *This can be done by decreasing* the amount of ketone from 5 to 2 ml., and by employing a cuvette which will give the maximum depth of liquid in the absorptiometer as described above.

The chief advantage of the method lies in the fact that only two glass containers are necessary: the blood tube in which the blood is collected and the extraction performed, and the cuvette for measuring the colour. The blood is weighed and not measured by pipette; and the D.N.O.C. concentration is expressed as microgrammes per gramme of blood.

By the method described, satisfactory recoveries of D.N.O.C. in 0·1 g. of blood can be obtained when the blood-D.N.O.C. concentrations are of the order of 5 µg. per g.

SIGNIFICANCE OF D.N.O.C. IN URINE

It has been suggested that the estimation of D.N.O.C. in the urine might prove useful as a guide to the amount of D.N.O.C. absorbed by persons at risk. Study of the available data indicates that under certain conditions there may be a correlation between blood and urine D.N.O.C., but it is unlikely that this would be close enough for practical use. Routine blood-D.N.O.C. estimation is the method of choice for assessing the risk of poisoning in persons using D.N.O.C.

The possibility of using a simple test for D.N.O.C. in a "grab" sample of urine has been considered.

The colour of low concentrations of D.N.O.C. in alkaline urine is not intense enough for even approximate estimation by the block comparator technique described by Cole (1933). There are several chemical tests, but these include complicated reactions involving formation of coloured complexes from unidentified metabolic end-products (Derrien 1917, Meyer and Drutel 1935, Fischer 1938). The method described by Fischer (1938) depends on the production of a purpurate derivative from unchanged D.N.O.C. and D.N.P. by the action of potassium cyanide. The sensitivity of the test is probably inadequate for usual routine testing since it has been suggested that it could be used for quantitative estimation of quantities of D.N.O.C. and D.N.P. in concentrations of the order of 0·2–1·5 mg

Some attempt has been made to correlate the "stabilised" blood-D.N.O.C. level with the urinary excretion by detailed examination of the results obtained from experiments on volunteers (Harvey et al. 1951) and in the spray operator described by Pollard and Filbee (1951). The "stabilised" blood-D.N.O.C. concentration is reached not less than 8 hours after the last exposure to D.N.O.C.

After absorption of small quantities of D.N.O.C. at regular intervals there appears to be a general correlation between 24-hour urinary excretion and the blood-D.N.O.C. level at the end of the 24 hours. In a case of poisoning high blood-D.N.O.C. concentrations showed some correlation with urine-D.N.O.C., although there were some misleadingly low 24-hour excretions (Pollard and Filbee 1951). Thus about 2 mg. D.N.O.C. was excreted in 24 hours for a corresponding blood-level of 25 µg. per g., and two consecutive quantities of 7 mg. for blood-D.N.O.C. levels of 21 µg. and 23 µg. per g.

Examination of the D.N.O.C. content of every urinary voiding during the dosing and postdosing periods of the experiments described by Harvey et al. (1951) shows that it is not possible to correlate any single urinary D.N.O.C. value with blood-D.N.O.C. concentrations. The only fractional values of the 24-hour sample which show any correlation with blood-D.N.O.C. levels are those obtained by combining the last excretion at night, from 11 P.M., with those up to and including the first in the morning. These combined D.N.O.C. values are approximately one-third of the total 24-hour excretion (fig. 2). Examination of the concentration of D.N.O.C. in the urine of different subjects showed that considerable scatter may occur. Thus from a mean blood value of 16·8 µg. per g. the urinary excretion of five volunteers ranges from 0·3 to 1·3 mg., and for a blood-D.N.O.C. level of approximately 5·0 µg. per g. the urine range is 0·2–0·35 mg.

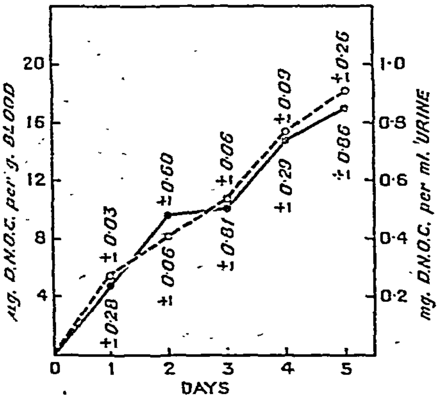

Fig. 2—Correlation between blood and urine D.N.O.C. values during dosing of five volunteers. Black circles = mean blood-D.N.O.C. values ("stabilised" values). White circles = mean urine-D.N.O.C values from 11 p.m. to first morning voiding. Standard error of mean is shown at each plotted mean.

No correlation exists between the blood and urine D.N.O.C. concentrations at the low levels recorded after the period of dosing.

It is therefore impossible to recommend the use of such fractional samples of urine for accurate assessment of the absorption of D.N.O.C. and the concentration of D.N.O.C. in the blood.

SUMMARY

A method is described for collecting 0·1–0·2 g. of blood for analysis of D.N.O.C. content by a modification of Parker's (1949) method.

With simple and readily available equipment 5–20 µg. D.N.O.C. per g. of blood can be estimated with reasonable accuracy.

The estimation of D.N.O.C. in "grab" samples of urine is not a reliable guide to the blood-D.N.O.C. level.

I wish to thank Dr. Donald Hunter, director of the department, for encouragement; Dr. P. Lesley Bidstrup, Dr. J. A. L. Bonnell, and Mr. E. King for many helpful discussions; and Miss Jean Peal and Mr. K. E. Carling for their invaluable and accurate technical assistance.

References at foot of next column

DIABETIC ACIDOSIS WITHOUT KETONURIA

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Richardson (1932), in America, described a case of diabetic acidosis with no acetone or diacetic acid in the urine. He stated that this condition had been known for some years; yet present-day knowledge of it appears to be very restricted, and it is possible that many physicians are unaware even that it exists.

Joslin (1945), emphasising the danger of giving glucose in diabetic coma, mentioned that a boy, aged 19, was in diabetic coma without any acetone or diacetic acid in his urine; unfortunately Joslin did not enlarge on this. Other cases have been published (Root 1946, Oliver 1926, Argy 1925, Warburg 1925, Paddock 1924, and Rosenbloom 1915). Coburn (1930) stated that ketosis without ketonuria occurred in 6 (16%) of his patients before 1923, and in 15 (16%) of those treated with insulin since that year, but these high figures included cases in which ketonuria was absent only temporarily, being preceded and followed by normal excretion of ketones.

As Richardson (1932) emphasised, failure to recognise this condition promptly may lead to the patient's death; so it is important that the absence of ketonuria should not prevent early and vigorous treatment of the diabetic acidosis.

CASE-RECORD

A married woman, aged 62, was admitted to hospital on June 12, 1951, in coma and with the history that, five days before admission, she had had an attack of diarrhœa and vomiting, which had left her very weak, and she then went gradually downhill. Her doctor had obtained a history of recent thirst and polyuria, and on testing the urine he found it loaded with sugar.

On examination soon after admission she was extremely obese and almost comatose, but she responded to painful stimuli. She had a dry red "raw-beef" tongue, and her skin was dry and inelastic. Air hunger was present, and acetone could be smelled in the breath. Her pulse-rate was 104 per min., temperature 99°F, respirations 28 per min., and blood-pressure 155/120 mm. Hg. Apart from absent knee-jerks there were no other physical signs, the plantar responses being flexor. The urine was loaded with sugar, but there was no ketonuria at any time. The clinical picture strongly suggested diabetic coma, and the blood-sugar level was 522 mg. per 100 ml.

Treatment with soluble insulin and intravenous glucose and saline solution was started, but the patient did not respond and died a few hours after admission.

Necropsy Findings.—The stomach was acutely dilated, and the lower lobes of both lungs were collapsed owing to regurgitation of stomach contents into the trachea. The kidneys had a thin cortex with poor differentiation between cortex and medulla, the surface of the kidneys being somewhat granular. The brain was normal apart from atheroma of the basilar arteries, and there was moderate atheroma of the coronary arteries. Histologically a moderate degree of renal arteriosclerosis was found.

DR. HARVEY: REFERENCES

Bidstrup, P. L., Bonnell, J. A. L., Harvey, D. G. (1952) *Lancet*, i, 794.
Cole, S. W. (1933) Practical Physiological Chemistry. Cambridge; p. 26.
Derrien, Y. (1917) *Bull. Soc. Pharm. Bordeaux*, no. 3.
Fischer, W. (1938) *Z. anal. Chem.* 112, 91.
Harvey, D. G., Bidstrup, P. L., Bonnell, J. A. L. (1951) *Brit. med. J.* ii, 13.
King, E. J. (1946) Micro-analysis in Medical Biochemistry. London; p. 124.
Meyer, A., Drutel, H. (1935) *Bull. Soc. Chem. biol., Paris*, 17, 1455.
Parker, V. H. (1949) *Analyst*, 74, 646.
Pollard, A. B., Filbee J. F. (1951) *Lancet*, ii, 618.

DIAGNOSIS

Neither plasma-carbon dioxide nor blood-ketone determinations were made in the present case, but the following evidence establishes the diagnosis of diabetic coma beyond reasonable doubt.

There was a characteristic history of thirst and polyuria, with a gradual lapse into coma, presumably hastened by the attack of gastro-enteritis five days previously, this being one of the commonest exciting causes of diabetic coma. Physical examination showed many significant features. Typical Kussmaul respiration was present, and acetone was smelt in the breath. The tongue was of the "raw-beef" variety, which according to Graham (1946) is only present when the patient is desiccated as a result of great polyuria; and the dry inelastic skin was further evidence of considerable dehydration. The knee-jerks were absent and the plantar responses flexor, these being common findings in diabetic coma. Glycosuria was heavy, and the blood-sugar level was very high, being over 500 mg. per 100 ml. The acute dilatation of the stomach seen post mortem is not infrequently found, being possibly secondary to the polydipsia; and the regurgitation of stomach contents into the lungs no doubt hastened death.

Other causes of coma associated with hyperglycæmia and glycosuria, such as cerebral hæmorrhage, subarachnoid hæmorrhage, brain-stem lesions, and meningitis, were definitely excluded by the necropsy findings.

DISCUSSION

Richardson (1932) gave three explanations for the absence of ketonuria:

(1) *Dehydration.*—In diabetic acidosis the base is diminished, and this reduction becomes more pronounced with dehydration. Richardson postulated that there may not be sufficient base to spare for the excretion of ketones which are in excess in the blood.

(2) *Partition of the Ketones.*—Richardson asserted that commonly more than half, and sometimes more than 90%, of the ketone bodies in the urine are present as β-hydroxybutyric acid, leaving a relatively small amount as acetone and diacetic acid, and that it is possible that all the ketones may exist as β-hydroxybutyric acid. In such cases the amount of acetone and diacetic acid in the urine may be too small to give a positive reaction with our clinical laboratory tests.

(3) *Pathological changes in the kidneys* may impair the excretion of ketones, but Richardson considered this problematical.

Warming-Larsen (1949) stated that, at a certain stage of diabetic coma, there may be not only no ketonuria but also no glycosuria, despite very high levels of both sugar and ketone bodies in the blood. He assumed that this is due to the reduced rate of filtration, all the ketone bodies and glucose excreted being actively reabsorbed into the kidney tubules. He made determinations of ultrafiltration (inulin clearance) in a series of healthy volunteers with inanition ketonæmia, and stated that the excess ketones in the blood leads to their presence in the glomerular ultrafiltrate, and then the ketone bodies are actively reabsorbed into the tubules of the kidney, with an upper limit to the ability of reabsorption. He stated that there seems to be a diminution in the rate of ultrafiltration simply because of the dehydration. Thus the absence of ketonuria even at very high blood-ketone levels is explained by the great reduction in the rate of filtration, and the kidneys can easily reabsorb the total amount of ketone bodies in the blood, so long as the figure of maximal reabsorption is not exceeded, which figure is calculated as the product of the ultrafiltration and the percentage of ketone bodies in the ultrafiltrate.

These various theories are open to criticism. The theory depending on reduced base is incorrect; for, though it is true that some of the ketone bodies are excreted along with the base, nevertheless some of the ketone acids, because of their weak acid character, are excreted as free acid in a highly acid urine, thus sparing base. As regards the theory of partition of the ketones, there is no proof that the urine in diabetic acidosis without ketonuria contains large quantities of β-hydroxybutyric acid, for which there is no simple urine test, and anyway how can it be possible for acetone to be excreted in the breath and yet when the blood reaches the kidneys only β-hydroxybutyric acid is present? Further criticism can be made by citing Rosenbloom (1915), who in five years saw three cases of diabetic coma without acetone, diacetic acid, or β-oxybutyric acid in the urine. The theory of diminished rate of filtration is feasible, but why does this not happen more often in diabetic acidosis, especially in cases with severe oliguria; surely here the rate of filtration is very low, yet acetone is almost invariably found in the urine of these patients. Warming-Larsen supported his theory with experiments on healthy persons, not on diabetics whose chemical and anatomical pathology is so deranged. There is, however, some support for Warming-Larsen in the writings of Coburn (1930), who described several cases where acetone disappeared from the urine before the onset of anuria. Coburn considered that failure to excrete acetone bodies seemed to be the harbinger of renal shut-down, and it is possible that a diminished rate of filtration was responsible for the disappearance of ketonuria in his cases, for ketonuria reappeared with the establishment of diuresis.

Now we are left with the theory that Richardson considered problematical—that pathological changes in the kidneys are responsible—and it may not be without significance that the case reported here shows definite evidence of kidney damage. Incidentally the renal histology was quite different from that found in the kidneys of diabetics by Kimmelstiel and Wilson (1936), with whose syndrome no similarity can be found.

The theory of pathological changes in the kidney is supported by Root and Marble (1946), who were of the opinion that only in cases in which there is associated renal block does one see a negative test for acetone bodies; by Warburg (1925), who described three cases which he thought were due to complicating renal insufficiency; and by Argy (1925), in whose case chronic parenchymatous and diffuse nephritis was found post mortem, there being advanced fatty degeneration and necrosis throughout, and Argy thought that the extensive renal pathology might explain the absence of ketonuria. It is possible that more than one theory is at least partially correct; for instance, a diseased kidney may prevent the excretion of more than a small amount of acetone, which is then reabsorbed by the kidney tubules.

Regrettably all the explanations are theoretical, and the reason for diabetic acidosis without ketonuria therefore remains uncertain. F[illegible] [illegible]rely academic, provided that the [illegible] are not disregarded. *Any patient who has the symptoms of diabetic acidosis must be treated urgently for that condition,* whether ketones are present in the urine or not; and, if the possibility of absent ketonuria is borne in mind, no patient should be lost through wrong or belated diagnosis.

SUMMARY

A case is reported illustrating the rare occurrence of diabetic acidosis without ketonuria.

The various theories propounded to explain this phenomenon are related and criticised.

The importance of early treatment of this condition is stressed.

I am indebted to Dr. T. Robson for permission to publish this case, and to Dr. T. K. Owen who did the necropsy.

References at foot of next column

EXTENSIVE RESECTION OF THE SMALL BOWEL

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Resection of the small intestine involving more than a few inches is usually the result of mesenteric thrombosis or embolism. Such cases have a high immediate mortality, and the late results are often disappointing. The following case is unusual and encouraging in that the after-effects of an extensive resection of small bowel are relatively slight and are not a serious disability or inconvenience to the patient.

CASE-RECORD

A man, aged 57, weighing 7 st. 1 lb., was admitted to Sefton General Hospital on June 29, 1951. He had had a gastro-enterostomy performed twenty years previously for duodenal ulcer. For several years he had had periodic central abdominal pain coming on about two hours after food and relieved by vomiting, which was often self-induced. The present attack had lasted a week.

He was thin and obviously in pain. There was tenderness in the umbilical region but no rigidity. No other abnormal physical signs were detected. Recurrent peptic ulceration was provisionally diagnosed.

Investigations.—A fractional test-meal showed complete absence of free acid. Bile was present throughout. The resting juice volume was 10 ml. Hæmoglobin was 99%. The fæces did not contain any occult blood.

Progress.—The symptoms subsided on a peptic-ulcer régime, but several days after admission the patient had severe persistent central abdominal pain and vomiting and developed considerable shock. His abdomen became distended and tympanitic, with generalised tenderness and rigidity. Bowel sounds were absent. Blood-transfusion and gastric suction were started and laparotomy was undertaken.

Operation.—The abdomen was opened through a right paramedian incision. The peritoneal cavity contained foul bloodstained fluid. Gangrenous small intestine presented. A tight band of omentum was encircling the root of the mesentery and causing strangulation, the mesenteric veins being distended with blood-clot. The entire small intestine, except 2 ft. of jejunum just distal to the gastro-enterostomy stoma and the last 3 in. of ileum, was gangrenous.

The omental band was divided, the gangrenous bowel resected, and an end-to-end anastomosis made between the jejunum and the ileum. At the end of the operation there was about 2 ft. of small intestine between the stomach and the cæcum. The patient's condition, which was very poor when the abdomen was opened, improved considerably after the resection. Gastric suction and intravenous fluid were continued after operation.

Postoperative Course.—The bowels opened spontaneously on the fourth day, and after this the patient was given a high-protein diet, supplemented with vitamins. Twelve days after operation he weighed 6 st. 9 lb. and the bowels were acting four or five times daily, the stools being semi-fluid and pale. The fæces contained an excess of fat (mainly neutral fat and fatty-acid crystals with a few soap crystals), a few undigested meat fibres, and an occasional starch granule. Five weeks after the operation he was on a full diet and a twenty-four specimen of fæces showed adequate fat-digestion but diminished fat-absorption:

Total fat	41·65 g.	per 100 g. of dry fæces.
Split fat	30·5 g.	
Unsplit fat	11·15 g.	

Of the fat 73% was split and 27% unsplit.
Total weight of fæces was 644 g., of which 81·7% was water.
Total weight of fat in specimen was 49 g.

Examination of the blood showed that it contained 25 mg. of non-protein nitrogen per 100 ml., Hb 78%, red cells 3,900,000 per c.mm., total plasma-protein 5·3 g. per 100 ml., and serum-calcium 9·2 mg. per 100 ml.

Six weeks after operation a barium meal produced the following radiological report:

> "Posterior gastro-enterostomy. The stoma functions normally. The duodenal cap shows persistent deformity due to chronic ulceration. A large portion of the small bowel has been resected and there is only about two or three feet of the jejunum remaining. Barium is noted in the cæcum in 40 minutes. The large bowel appears normal and is almost completely empty in 24 hours."

The patient was discharged from hospital about seven weeks after the operation. He was advised to take a high-protein low-fat diet supplemented with vitamins. His weight on discharge was 7 st. 4 lb.

Follow-up.—Three months after operation the weight was 8 st. 4 lb., and a month later 8 st. 10 lb.

DISCUSSION

The term "extensive resection" is applicable where 80 inches or more of small intestine is excised (Haymond 1935). This means a removal of about a third of the usual length of the small intestine, and is the greatest length that can be resected with subsequent normal intestinal function. Since the length of the small bowel varies, the amount left is of more significance than the amount resected. From the nutritional point of view the ultimate progress is better where jejunum is retained. Carbohydrate and protein are absorbed mainly from the jejunum, and fat from the ileum.

Compensatory changes develop in cases of extensive bowel resection. There is a delay in gastric emptying with prolongation of gastric digestion. Flint (1912) performed enterectomies in dogs and found that the remaining bowel increased in diameter to about twice the normal size, and the absorbing surface increased by 400%.

The after-effects of extensive small-bowel resection are as follows:

(1) *Loss of weight* due to defective absorption of fat. Digestion of fat is usually adequate, but takes place largely in the colon, from which no fat is absorbed. There may be an associated deficiency of fat-soluble vitamins.

(2) *Diarrhœa* tends to improve with time as compensatory changes develop. The fæces contain an excess of fatty acids, which combine with calcium to form soaps, with the result that the stools are foamy.

(3) *Hypocalcæmia* and *tetany* have been described (Cosh 1944). These symptoms are especially liable to develop when there is gastric achlorhydria. Acid facilitates the absorption of calcium as calcium chloride. In an alkaline medium calcium combines with fatty acids and is passed in the stools.

The present patient has but few after-effects. Although denied both the compensation of delayed gastric emptying and the absorbing surface of the duodenum, owing to his previous gastro-enterostomy, he gained 1 st. 9 lb. in the four months after the resection. He still appears very thin and must be regarded as underweight, because before the resection he had dyspepsia and vomiting for several years. The bowels act four or five times daily, the consistence of the stool varying from liquid to semi-solid. His chief complaint is that the call to defæcate comes suddenly and must be obeyed immediately. He has gastric achlorhydria but no calcium deficiency and no evidence of vitamin lack. The digestion and absorption of proteins and carbohydrates seem to be normal.

DR. HENNEMAN: REFERENCES

Argy, W. P. (1925) *Boston med. surg. J.* 193, 1236.
Coburn, A. F. (1930) *Amer. J. med. Sci.* 180, 178.
Graham, G. (1946) *In* Price, F. W., A Textbook of the Practice of Medicine. 7th ed., London; p. 443.
Joslin, E. P. (1945) *New Engl. J. Med.* 232, 219.
Kimmelstiel, P., Wilson, C. (1936) *Amer. J. Path.* 12, 83.
Oliver, T. H. (1926) *Lancet*, i, 750.
Paddock, B. W. (1924) *J. Amer. med. Ass.* 82, 1855.
Richardson, R. (1932) *Med. Clin. N. Amer.* 16, 257.
Root, H. F. (1946) *In* Joslin, E. P., The Treatment of Diabetes Mellitus. 8th ed., Philadelphia; p. 440.
— Marble, A. (1946) *Ibid.*
Rosenbloom, J. (1915) *New York med. J.* 102, 294.
Warburg, E. (1925) *Acta med. scand.* 61, 301.
Warming-Larsen, A. (1949) *Ibid*, suppl. no. 234, p. 326.

He is free from pain and is carrying on his occupation of shopkeeper.

I wish to thank Mr. W. M. Beattie, under whose care the patient was admitted, for permission to treat the case, and Mr. J. Cosbie Ross for help and advice in the preparation of this report.

REFERENCES

Cosh, J. A. (1944) *Lancet*, ii, 596.
Flint, J. M. (1912) *Bull. Johns Hopk. Hosp.* 23, 127.
Haymond, H. E. (1935) *Surg. Gynec. Obstet.* 61, 693.

Reviews of Books

Cleft Lip and Palate

W. G. HOLDSWORTH, M.B., F.R.C.S., surgeon, Rooksdown Hospital, Basingstoke. London: Heinemann Medical Books. 1951. Pp. 126. 35*s*.

AFTER describing the normal anatomy of the lip and palate and the muscles concerned with the creation of an efficient oronasal sphincter, Mr. Holdsworth reviews the development of these areas and classifies the abnormalities to be expected. In the rest of the book he describes various techniques which have been used or may be used; but he does this so impartially that it will be difficult for the inexperienced reader to decide which methods are commonly applicable, and what their merits and demerits may be. Thus the Langenbeck method receives as much attention as the so-called Wardill technique, and no hint is given as to when one should be preferred to the other. In all reparative surgery, of course, the choice of a method very largely depends on the surgeon's own feelings; but there are times when advice is welcome. The book is, however, very well produced and very well illustrated, and contains a wealth of information.

Chiropodial Orthopædics

FRANKLIN CHARLESWORTH, F.CH.S., consultant chiropodist, Hope Hospital, Salford. Edinburgh: E. & S. Livingstone. 1951. Pp. 255. 25*s*.

THE provision of satisfactory supports for the overstrained or defective foot has always presented a difficult problem. To be really effective, supports must not only fit exactly but should be designed individually for every foot; the standardised methods of the instrument maker can never be fully satisfactory. To meet this difficulty, Mr. Charlesworth has found ways of manufacturing supports of a semipermanent kind, replacing the usual pads and strapping, which can be made for each individual patient by the chiropodist. He has shown much initiative and ingenuity in developing these techniques, and he describes the methods clearly in this book. The making of these appliances is outside the compass of the ordinary orthopædic mechanic, and the question thus arises: how are they to be provided within the framework of the health service? Bad feet are a common disability, and Mr. Charlesworth's methods seem to promise prospects of the relief of much pain and disablement. The solution may well lie, as Mr. Charlesworth himself thinks, in the further development of chiropodial units, run in association with the orthopædic departments of our larger hospitals. His book can be recommended to all who have anything to do with the care of the feet.

Liver Injury

Transactions of the Ninth Conference, April 27 and 28, 1950, New York. Editor: F. W. HOFFBAUER, M.D. New York: Josiah Macy, Jr., Foundation. 1951. Pp. 232. $3.00.

THE interest of this series is well maintained. Aspiration biopsy of the liver is now an accepted diagnostic procedure in most large hospitals, and in this volume the histological differences between hepatic material obtained before and after death, the representative value of such small biopsies, and the correlation of morphological findings with results of biochemical tests are well discussed. Recent studies on hepatic vascular physiology and lymphatics are also included. The section on nutritional disease of the liver is interesting, but already almost out of date. The book is well produced and illustrated but would have benefited by more careful editing. Moreover, verbatim reporting, though often entertaining and easy to read, is not always either lucid or concise.

Chronik der Kinderheilkunde

ALBRECHT PEIPER, director of the University Children's Clinic, Leipzig. Leipzig: Georg Thieme. 1951. Pp. 277. D.M. 20.

Professor Peiper's history of pædiatrics, which he has dedicated to the late Prof. A. Czerny, his teacher, is an interesting and original book. He briefly traces pædiatrics through the ages to modern times, discussing its social aspects and its scientific background. Accounts of the history of diseases such as scurvy and rickets lead naturally to historical sketches of the infectious diseases; and some discussions on witchcraft, beds, cradles, and swaddling round off a collection of short essays which have given the author pleasure to write and should give others pleasure to read.

Quelques aspects de la gynécologie actuelle

R. BOURG, *professeur à la Université Libre de Bruxelles.* Paris: Masson. Pp. 172. Fr. 900.

SOME small books can say a great deal, but though the literary style of this one is beautifully concise and clear, and some of the brief descriptions could hardly be bettered, it actually says very little. Professor Bourg does not claim, however, to have covered the subject fully. Differences of outlook in the teaching of gynæcology in this country and in parts of the Continent are noticeable. Most of the teaching of clinical medicine on this side of the Channel is based on pathology, which is sound enough and helps to reduce empiricism in treatment. Again British gynæcology at its worst almost boils down to "Lump, cut; no lump, no cut"; but perhaps this highly extraverted outlook has its good points. This book contains long lists of diagnostic methods, including cœlioscopy, culdoscopy, salpingography, and the evaluation of adnexal cysts, scrapings, snippets, and smears; otherwise it concerns itself mainly with the non-surgical aspects of gynæcology.

L'année thérapeutique en ophtalmologie

Vol. 2. Editors: G. E. JAYLE and A. DUBOIS-POULSEN. Paris: L'Expansion Scientifique Française. 1951. Pp. 397. Fr. 2000.

THE second annual therapeutic review in ophthalmology consists of twenty-one contributions.

Some of these—like the sections on ophthalmology and dental care by Jean Sedan, and on antihæmorrhagic vitamins by Bietti—are as much essays in pathology as reviews of treatment. Most chapters are general surveys and a few deal with specific agents. Thus Bessière gives a largely historical account of interstitial keratitis, whilst François discusses the treatment of chronic uveitis, and Legrand the treatment of keratoconus. There are similar reviews on occlusion of the retinal vessels, on diabetic retinopathy, on migraine, and on squint. Miller, Ourgaud, and Viallefont deal respectively with streptomycin, di-isopropyl fluorophosphonate (D.F.P.), and chemotherapy in ocular tuberculosis. Most of the contributions draw largely on French publications.

The Queen Charlotte's Textbook of Obstetrics (8th ed. London: J. & A. Churchill. 1952. Pp. 532. 37*s*. 6*d*.).—This old-timer, written by the clinical staff of Queen Charlotte's, has been developing some of the rigidity common in advancing age. The task of Mr. S. G. Clayton, F.R.C.S., F.R.C.O.G., the editor, has therefore been to coördinate and limber up the work, and so restore to it the pliability of youth. The sections on toxæmia, medical disorders of pregnancy, and the normal and abnormal puerperium, and the section on psychiatry in relation to reproduction, have all been rewritten—the last somewhat sketchily, unfortunately. The opinions expressed, and the methods of treatment described, the preface says, are those now taught in Queen Charlotte's Hospital; and this is recommendation enough. It is remarkable, however, that the word "relaxation" does not appear in the index, and that no mention whatever is made of this technique in the sections on the management of pregnancy and labour. In the interest both of their future patients and their own credit with the examiners, students should supplement their reading with textbooks more in line with modern opinion on this topic.

THE LANCET

LONDON: SATURDAY, APRIL 19, 1952

Cross-infection in the Wards

HOSPITAL-gangrene, once so destructive, has been wiped out by precise aseptic ritual in the operating-theatre. LISTER, confronted with inept hospital buildings, the custom of centuries, and the hostilities, doubts, and inertia of colleagues and administrators, must often have despaired of bringing this about. Nowadays doctors, administrators, and hospitals are all more accessible to new ideas; but whereas doubts and hostilities, like hospital gangrene, have yielded to modern methods, hospital inertia has proved wonderfully resistant. Since 1941, as Dr. J. W. D. GOODALL reminds us on another page, the Medical Research Council have been issuing reports on the prevention of cross-infection in the wards. Yet his study of 24 wards in eight hospitals, made in 1950, shows how little their wisdom had been regarded up to that time; and there is no reason to suppose that methods have since changed radically.

The incidence of infection in 13 wards where records were kept was about 10% for the whole group of 5095 patients; but it ranged from 3% in one general surgical ward to 21% in a children's ward. The infections most common among children were colds and other respiratory infections, septic conditions, and acute infectious fevers. In the maternity wards urinary and puerperal infections were seen most often, with phlebitis and mastitis taking second and third place. Responsible organisms included *Bacterium coli*, *Staphylococcus aureus*, *Streptococcus fæcalis*, and a hæmolytic streptococcus. In surgical wards these were joined by *Proteus vulgaris* and *Pseudomonas pyocyanea*, diphtheroids, and pneumococci. Among 223 staff (45 doctors, and the rest mainly nurses) colds accounted for 60% of the infective illnesses, but sore throats and septic conditions were also common, the usual organisms being *Staph. aureus*, *Staph. albus*, *Strep. pyogenes*, *and Strep. pneumoniæ*. The effects of these infections on the patients ranged from the passing inconvenience of a head cold to the much more serious discomforts of wound infection, phlebitis, and abscess. In 3 surgical wards 40 patients out of 851 had to stay longer in hospital because of an acquired infection, the average increase of stay per infected patient being 21 days. In one thoracic ward the increase was estimated at 60 days.

These figures suggest that, like LISTER's contemporaries, we have fallen into the way of accepting low standards as a necessary evil. Hardly any of the measures to prevent cross-infection recommended by the Medical Research Council were in operation in the eight hospitals selected for study. Thus the distance between the centres of the beds varied considerably, but the average was only 7 ft, whereas the council advises a separation of 8 ft. Again, most of the wards were of the large open type, which the council has described as obsolete, and nearly half of them had no single rooms, though a few were subdivided by partitions. They were ill-equipped in other ways: thus the sluice-rooms often housed a shocking hotch-potch of clean and dirty gear, and the patients' lavatories generally opened off them. Baths were not adequately sterilised after use, mainly because baths are almost impossible to sterilise adequately; presumably they should be replaced by showers or fitted with some specially designed sterilising equipment. In one ward the nurses had no basin in the ward in which to wash their hands. Only one ward had a modern sink-unit, provided with a second sink for rinsing dishes when washing up. Refrigerators used for storing milk and butter also contained pathological specimens. Only 2 out of 24 wards had treatment rooms where dressings could be done; and neither of these had controlled ventilation. These defects of structure and equipment were naturally a great handicap to the staff, and made the prevention of cross-infection more difficult; but it is evident from Dr. GOODALL's study that neither doctors nor nurses had a sufficiently exacting technique, and that the prevention of infection was not kept clearly enough in view. It is well to bear in mind that the behaviour of the nurses is almost bound to reflect the behaviour of the doctors—witness the fact that in one ward masks were not worn for dressings because the surgeon in charge did not believe in masks. There is no hope of getting the nurses to observe a stringent technique if they see it continually infringed by the doctors; and they are quite right: what would be the use? The prevention of infection, whether in the operating-theatre or the ward, depends on a high sense of personal obligation in every member of the team. This sense is second nature to doctors in the theatre: mordant chiefs developed it for them in their student years. But in the wards they had nothing like the same drilling, and there the old Adam leaps up again. "If a doctor is unwell," Dr. GOODALL says, "whether with a cold or anything else, he is a law unto himself. Generally he continues to do his ward rounds." His motives in so doing may be admirable; but he disseminates, along with his streptococci, a bacteriologically bad example.

The other great enemy of good technique is custom. "We have always done it like this," has terrible force among the British. Dr. GOODALL found sputum cups being emptied straight down the sluice, though the Medical Research Council insisted, almost ten years ago, that the contents should first be disinfected. In some wards the cups were then boiled, in some they were not. Methods of dealing with bedpans varied greatly: in 2 wards only were they sterilised by steam in special equipment, in 2 they were boiled, and in the rest they were usually "disinfected" with 1 in 20 lysol or phenol once daily. Syringes were not always sterilised effectively, nor were sharp instruments; on the other hand, dressing-bowls, by a time-honoured custom, were boiled for twenty minutes when two would have done. Masks of the type recommended by the M.R.C.—six layers thick, or incorporating an impermeable layer—were not seen, though various other types, many of them ineffectual, were in use. Dust suppression, though recommended, both by the council and by many other authorities, was seldom attempted.

Bedclothes were not oiled, because this required a special washing-machine. Oiling of the floors had been tried in a few wards but given up because it damages the rubber tyres of ward furniture, and makes the floors slippery. Matrons probably feel that nurses run quite enough risks from slippery hospital floors without being invited to skid on an oiled surface; moreover, the grubby appearance of an oiled floor, and its trick of soiling any fabric which touches it, makes it objectionable to ward sisters. Nurses may have to kneel on the floor to empty lockers; it irks them to rise with a dirty apron. It should be possible to find a substance which will make a floor tacky but not slippery, which will not damage rubber, and which has not the peculiar soiling qualities of dusty oil.

Some failures to prevent cross-infection in the wards could be avoided by better equipment; but Dr. GOODALL's study makes it clear that, like most things in medicine, success depends in the main on people. This is the reason why it will not do to teach student nurses nothing but nursing techniques: they must have a sound drilling in the prevention of infection, backed by enough knowledge of bacteriology to make them think imaginatively about what they are doing. They must learn these things from the doctors who lecture to them, and the doctors must devise special lectures with this end in view. It is high time we took a great deal more interest in what the student nurse is taught; for if she is not taught the right things, and taught them *intently* and *persistently* enough, she will be a weak and dangerous member in the preventive team. Again, the medical student should be given a far more exacting conscience about his behaviour in the ward, so that when he finally enters it in a position of responsibility he will not corrupt young nurses by slovenly habits. He who dresses a wound with a scrupulous no-touch technique while distributing a virus infection to a wardful of children, or wags a septic finger at a nurse while impugning her method of sterilising instruments, does little to further the cause of preventive medicine.

Myasthenia Gravis and the Thymus

SAUERBRUCH, in 1917, was the first to remove the thymus in a case of myasthenia gravis. It was not until 1939, however, that this operation was again described, by BLALOCK and his associates;[1] and since then other notable surgical series have been those of EATON,[2] HARVEY,[3] VIETS,[4] and HOLMES SELLORS.[5] All these surgeons, with an almost equal experience of about 30 patients each, have seen remarkably good results but have also had their disappointments. Unlike the others, KEYNES,[6] from his much larger series of 125 thymectomies, concluded that a neoplastic thymus carried a worse prognosis and required a more careful approach with preliminary irradiation; and the report by Dr. ROSS in this issue is based on the result of 100 consecutive thymectomies carried out by KEYNES, the only selection being the omission of the patients with benign or malignant tumours of the thymus.

Apart from the large number, the series described by Dr. ROSS has the advantage of a longer follow-up period than any previously described. The outstanding feature is that of these 100 patients no fewer than 41 are placed in the A group—i.e., they have no residual symptoms of myasthenia and are leading normal lives without the use of any drugs. The average period of observation for this group is 7·5 years; and 22 of the patients classed A in KEYNES's 1949 report are included in the new series, while we are assured that none of the remainder of his A patients have shown any sign of relapse. 26 patients are in group B, with inconstant and minor symptoms and fit for a full scale of activities with no limitations due to myasthenia gravis. These may be added to group A, giving a total of 67 excellent results out of 100. This confirms the great value of thymectomy, even if the further evidence of the 20 patients in group C is less certainly convincing. This group show considerable improvement, and they take less neostigmine with a response that equals or excels that before the operation. Only 6 patients are in group D, the total failures, and 7 have died. Other conclusions established are that a short history improves the outlook for thymectomy, while the age of the patient has no bearing on it.

This report makes out a strong case for thymectomy, suggesting that it is unsuitable only for patients with a long history or for those with a known tumour, who require preliminary irradiation. One unsettled question is why the failures are so much fewer than in other series. It seems possible that overlooked thymic tissue might explain failures and relapses. For instance, in the series reported by EATON et al. the less complete mediastinal exploration, without splitting the sternum, that was undertaken in 7 of the 15 patients may explain the less favourable results; and yet 2 of their patients improved strikingly although thymic tissue had deliberately been left behind owing to the dangers of removal. On the other hand HOLMES SELLORS saw a patient's condition improve considerably after the removal of a benign thymic tumour, and then relapse fatally some eighteen months later; and necropsy revealed no evidence of thymic remnant. This confusion may be resolved by NEVIN's[7] suggestion that lymphorrhages in the muscles may play a rôle similar to that of the thymus. His hypothesis would explain the relapses and failures that may follow effective removal of the gland. A further possibility should be kept in mind. The distribution of muscular weakness in myasthenia and its ready reversal by drugs are characteristic of a disorder of myoneural function, such as is seen also in curare poisoning or acute thyrotoxic bulbar palsy.[8] The pattern of myasthenia can therefore be due to other curarising agents than that suppressed by thymectomy. Endocrinology has moved a long way from the primitive concept of each disease being due to over-function or under-function of a single gland. We now recognise, for example, that a number of different disorders may lead to carbohydrate intolerance; and just as some diabetics do not benefit from insulin because they cannot use it, so some myasthenics may perhaps be

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1. Blalock, A., Mason, M. F., Morgan, H. J., Riven, S. S. *Ann. Surg.* 1939, 110, 544. Blalock, A. *J. thorac. Surg.* 1944, 13, 316.
2. Eaton, L. M., Clagett, O. T., Good, C. A., McDonald, J. R. *Arch. Neurol. Psychiat.* 1949, 71, 467.
3. Harvey, A. M. *Bull. N.Y. Acad. Med.* 1948, 24, 505.
4. Viets, H. R. *Brit. med. J.* 1950, i, 139.
5. Sellors, T. H. *Arch. Middlesex Hosp.* 1952, 2, 1.
6. Keynes, G. *Brit. med. J.* 1949, ii, 611.
7. Nevin, S. *In* Modern Trends in Neurology. London, 1951.
8. Laurent, L. P. E. *Lancet*, 1944, i, 87.

unaffected by thymectomy because they were not in fact hyperthymic.

While congratulating KEYNES on his outstanding results, we should gratefully remember MARY WALKER's discovery of the action of neostigmine, which made thymectomy possible and to which no fewer than 59% of KEYNES's patients are still indebted. Dr. Ross's comparison of surgical results with those of three medical series are a little unfair to modern medical treatment. KENNEDY and MOERSCH reported 87 cases which had never had any effective treatment; their series was intended as a standard for comparison with BOOTHBY's 82 patients, treated mainly with glycine (now given up) or, in a few instances, with small doses of neostigmine. Unfortunately, EATON's series does not happen to provide suitable data for comparison. Dr. Ross is handicapped here by the surprising scarcity of information on cases treated medically; but one thing is certain—that medical treatment still has a useful place in myasthenia.

Virus Pneumonia in Children

THE term "virus pneumonia" implies invasion by a virus of the terminal bronchioles and alveoli with consequent interstitial mononuclear reaction. Of the virus infections known to involve the lung in this way, measles is probably the commonest in children. Indeed, if this disease did not produce a rash, it might be classified among the virus pneumonias of childhood. The influenza viruses per se may cause pneumonia; but this is exceedingly rare, and usually they only pave the way for various bacteria. In children psittacosis seems to be mild and rare, and the pneumonia of Q fever is also very uncommon. In children, as in adults, when all the many known causes of pneumonia have been excluded, there remains a large number of cases in which no pathogenic agent can be directly demonstrated. Circumstantial evidence leaves little doubt that bacteria account for some of these. In others constitutional disturbance is slight, and upper respiratory catarrh is the only special feature; these cases resemble the "aspiration pneumonia" of adults, and there is no reason to suppose that any specific infective agent is at work. In a third group the illness begins, not with catarrhal symptoms, but with a cough or constitutional disturbance; and inquiry may reveal contact with a similar case about a fortnight earlier. In such cases treatment with penicillin and sulphonamides has no effect on the temperature; and serological examination shows a rising titre of cold agglutinins[1,2] and possibly of streptococcus MG agglutinins as well. There is good evidence that this last group is due to a specific virus or group of viruses. During the late war such an illness was fairly common in the Forces, but at the present time in this country it seems to be relatively rare in adults.

MACAULAY[3] reports cold agglutinins in raised titre in 26 out of 114 children most of whom had infections of the respiratory tract. He found a clear correlation between a raised cold-agglutinin titre and pulmonary involvement, but none with any other clinical or pathological change. For this there would seem to be two possible explanations: either, as he suggests, the raised titres indicate a non-specific reaction to pulmonary injury, or else these cases are examples of a specific infection with varied manifestations. The absence of other positive bacteriological findings and the extreme rarity of high cold-agglutinin titres in proven cases of pneumococcal pneumonia support the latter view. Moreover, it seems that in adults the virus or viruses that give rise to pneumonia with raised-cold-agglutinin titres may not uncommonly produce a more varied clinical picture than was at first thought. The onset may be gradual or sudden; the illness may be trivial or long and severe; relapses may occur; a polymorphonuclear leucocytosis is not uncommon, especially in the second and third weeks of the disease; the radiological appearances are very variable, and the whole of a lobe may be involved as in pneumococcal lobar pneumonia. More dramatic, but fortunately rare, manifestations are acute hæmolytic anæmia and erythema multiforme exudativum. There is some evidence that the agent causing this pneumonia in adults may in infants cause the syndrome of gastro-enteritis without pulmonary involvement.[4]

The presence of inclusion bodies in the epithelium of the respiratory tract of infants and children has been cited as evidence of virus infection. A number of different types have been reported. GOODPASTURE et al.[5] described intranuclear inclusions in the lungs in five cases of pneumonia of varied ætiology; these were morphologically distinct from those seen in herpes simplex and cytomegalic inclusion disease. A combination of intranuclear and cytoplasmic inclusions has been described in giant-cell pneumonia of infants and in measles by PINKERTON et al.,[6] who drew attention to the similarity of the pathological appearances to those seen in distemper in various lower animals. Cytomegalic inclusion disease is probably due to a human strain of the salivary-gland virus, which may involve various organs[7]; affected cells are considerably enlarged and contain both intranuclear and cytoplasmic inclusions. This infection is associated with a number of different clinical syndromes, including fibrocystic disease of the pancreas and a condition resembling whooping-cough. ADAMS[8] has reported outbreaks of "pneumonitis," affecting young infants and newborn babies, in which cytoplasmic inclusion bodies were found in the bronchial epithelium post mortem. Similar inclusions were found in nasopharyngeal smears from affected babies and the majority of contact adults, but they were seldom seen in control cases. It is not clear whether these bodies were the same as those detected in nasopharyngeal smears by a number of different workers before and since. MACAULAY found them in the majority of his cases; and LUDLAM[9] has demonstrated them in the squamous epithelium of the mouth and throat in each of over a hundred newborn infants. LUDLAM also found them in 31 out of 32 adults, but in much smaller

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1. Ames, R. G. *Cincinnati J. Med.* 1947, 28, 791.
2. Hodges, R. G., Scott, O. K. *Amer. J. Dis. Child.* 1949, 77, 123.
3. Macaulay, D. *Arch. Dis. Childh.* 1951, 26, 601.
4. Keitel, H. G. *J. infect. Dis.* 1950, 86, 219.
5. Goodpasture, E. W., Auerbach, S. H., Swanson, H. S., Cotter, E. F. *Amer. J. Dis. Child.* 1939, 75, 997.
6. Pinkerton, A., Smiley, W. L., Anderson, W. A. D. *Amer. J. Path.* 1945, 21, 1.
7. Smith, M. G., Vellios, F. *Arch. Path.* 1950, 50, 862.
8. Adams, J. M. *Amer. J. Dis. Child.* 1948, 75, 544.
9. Ludlam, G. B. *J. Path. Bact.* 1951, 63, 687.

numbers; and he suggests that they are derived from nuclear extrusions and may be regarded as an early stage in keratohyalin production.

The diagnosis of virus pneumonia is even harder in children than in adults. In serological work the interpretation of single specimens is notoriously difficult, and in infants this difficulty is increased by the presence of maternal antibodies and the uncertainty about the pattern of the infant's antibody response. The viruses of the "common cold," acute respiratory disease, non-bacterial exudative tonsillitis, and other upper respiratory infections may play a part along with influenza in the pathogenesis of bacterial pneumonias; but whether they themselves can cause disease of the lower respiratory tract in infants and young children is unknown. In older children with pneumonia, a rising titre of cold agglutinins seems to have the same significance as in adults, but inclusion bodies in the nasopharyngeal epithelium seem to have no specific significance.

Annotations

TUBERCULIN SURVEY

In the epidemiology of tuberculosis there are three important yardsticks—infection, morbidity, and mortality. In this country mortality-rates for tuberculosis have been recorded for over a century, and constitute the best measure of long-term progress. Notification, which has been compulsory since 1912, gives some measure of morbidity but is not complete. Estimates of the proportion of infected individuals—i.e., reactors to tuberculin—at different ages and in different areas have been lacking; but on evidence from Continental cities there was a general belief that childhood infection was universal in our towns in the earlier part of this century.

The results of the tuberculin survey of over 94,000 children and adolescents, published in this issue, go far to supply a measure of the level of infection in children and adolescents, and finally dispel any idea of universal childhood infection at the present time. The survey was suggested by the British Tuberculosis Association, and organised and analysed by the Medical Research Council, while the field work was done by medical staffs of chest clinics, mass-radiography units, and health departments. The 22 areas surveyed were selected to be as representative as possible.

Combining all areas and both sexes, the proportion of positive reactors increases with age from 14·5% at the age of 5 years to 66·6% at the age of 19–20. At the age of 5 the highest proportion of positives is found in rural areas—20·3% positive, compared with 13·5% in Northern urban areas and 9·3% in Southern urban areas. The percentage positive is highest in rural areas throughout school life; but shortly after school-leaving age the percentage positive in Northern urban areas approaches the figure for rural areas very closely, and by the age of 19–20 the highest percentage positive is found in Northern urban areas—73·6%, compared with 65% in rural areas and 59·3% in Southern urban areas. The Southern urban areas have the lowest percentage positive at all ages from 5 to 20. The increase in the proportion positive between various age-groups is best measured by the calculated "annual conversion-rates." These show an increase of 3–4% of positives for each year of life during school ages in Southern urban areas, but of over 5% in Northern urban and rural areas. Over school ages the conversion-rates are higher in all areas, reaching 12% in Northern urban areas, 7–10% in Southern urban areas, and 5–8% in rural areas. At these ages males show higher conversion-rates than females, in contrast to the greater mortality and notification rates in females at these ages. Comparison with the less representative figures of the Prophit Survey suggest that the percentage positive has fallen appreciably since the years before the war. For males aged 15–16 years the Prophit Survey in 1937–39 recorded 63% positive, compared with 40–55% found positive at this age in 1949–50. At the age of 18–19 years the Prophit Survey found 80–85% positive, compared with the 59–74% found in 1949–50.

The increase in the proportion positive with increase of age is to be expected. Higher figures for adolescent boys than for girls of similar age have been shown by most large surveys in other countries, and are usually attributed to the more adventurous nature of boys leading them to a greater number of social contacts. The most important differences shown are between the three geographical groupings: the differences between Northern and Southern urban groups presumably reflect the less satisfactory tuberculosis position in the North, as shown by mortality-rates, of which the rates for Scotland are the extreme example. The higher proportion of positive reactors to tuberculin in rural than in urban school-children reflects their much greater opportunities of drinking unpasteurised milk from tuberculous cows—opportunities which the great majority of the medical profession, with good reason, regard as highly dangerous.

ELASTOSIS DYSTROPHICA

Darier [1] gave the name "pseudoxanthoma elasticum" to a skin condition in which yellow, rounded, or linear discolorations appear, mostly in the flexures, with flaccidity of the skin. Histologically there is degeneration and fragmentation of the elastic tissue of the corium. This disorder has no relationship to xanthomatosis beyond the clinical similarity; so the terms "elastosis dystrophica," suggested by Böck,[2] or "elastosis dysplastica," suggested by Parkes Weber,[3] seem preferable. This uncommon familial malady is usually first recognised by the dermatologist or the ophthalmologist. The first symptom may be defective vision, due to retinal detachment caused by degeneration of the fibres of Bruck's membrane of the choroid. Grönblad [4] and Strandberg [5] first described the angioid streaks in the retina that indicate this degenerative process.

The general physician should be aware of this syndrome because it may include degeneration of the elastic tissue of arterial and arteriolar walls. When this happens the symptoms are most varied. According to Revell and Carey,[6] in order of commonness these are hypertension, intermittent claudication, angina pectoris, calcification of the peripheral vessels, gastro-intestinal hæmorrhage, psychic disturbance, epilepsy, thyrotoxicosis, and diabetes mellitus. Wolff et al.[7] have described a boy with pseudoxanthoma elasticum, who had fundal changes, absent peripheral pulses, intermittent claudication, and recurrent hæmorrhages. Miliary mottling was noticed in the lung-fields on radiographic examination; and possibly this was due to involvement of the interalveolar septa and of the small pulmonary blood-vessels. With electron microscopy the component fibrils seemed normal, despite their fragmented and irregularly whorled appearance on biopsy. This may support Hannay's [8] contention that the hypertrophied fibres found in the corium are not elastin but collagen which has undergone a physico-chemical change. It is significant, too, that calcification,

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1. Darier, J. *Mh. prakt. Derm.* 1896, **23**, 609.
2. Böck, J. *Z. Augenheilk.* 1938, **95**, 1.
3. Weber, F. P. Modern Trends in Dermatology. London, 1948; p. 315.
4. Grönblad, E. *Acta Ophthal. Kbh.* 1929, **7**, 329.
5. Strandberg, J. *Zbl. Haut-u. GeschlKr.* 1929, **31**, 689.
6. Revell, S. T. R., Carey, T. N. *Sth. med. J., Nashville*, 1948, **41**, 782.
7. Wolff, H. H., Stokes, J. F., Schlesinger, B. E. *Arch. Dis. Childh.* 1952, **27**, 82.
8. Hannay, P. W. *Brit. J. Derm.* 1951, **63**, 92.

which is a feature of pseudoxanthoma elasticum, is also common in collagen degeneration. On the other hand, it would be strange if the elastic tissue of the skin escaped when other elastic tissues are severely affected. It is possible that in the skin the collagen is affected to some extent as well as the elastin.

Pseudoxanthoma elasticum has to be differentiated from other forms of cutis laxa (for example, the Ehlers-Danlos syndrome), from neurofibromatosis, and from connective-tissue nævi. According to Prakken [9] the important distinctive features of connective-tissue nævi are their asymmetry without selective localisation, their relatively larger size, and the absence of associated systemic changes, ocular changes, or calcification.

RADIO-IODINE AS A THERAPEUTIC AGENT

IODINE is concentrated in the thyroid to a greater extent than any other atom is concentrated in any other organ; and thus the radioactive isotopes of iodine can be used to bombard the thyroid from within, without materially damaging other tissues. One of these isotopes—I^{131}—has the advantages of emitting both β and γ rays, of having a convenient half-life of 8 days, and of being relatively easily and cheaply obtained from the atomic pile. The β rays are highly lethal to cells at close range, but do not affect extra-thyroid tissue to any extent; while the γ rays enable concentrations of iodine to be readily located by a Geiger counter outside the body. In two clinical conditions—thyroid cancer and thyrotoxicosis—the removal of excessive thyroid tissue is highly desirable; and I^{131} might seem the ideal agent for effecting this removal without danger or discomfort to the patient.

For nearly ten years much time and effort have been given in America to realising this expectation. In this country we started later; but already enough experience has been gained to provide a picture of what happens when patients with thyroid disease are treated with radio-iodine. This experience was summarised at a meeting of the section of endocrinology of the Royal Society of Medicine on Feb. 27. It is evident that both in thyrotoxicosis and in thyroid cancer radio-iodine, in favourable circumstances, can do what is expected of it. Dr. E. E. Pochin, Prof. E. J. Wayne, and Dr. Russell Fraser, working independently, have all seen cases—numbered so far only in dozens—where thyrotoxicosis has been eliminated by such treatment. To the patient this seems almost too simple to be true: he merely has to drink a glass of water, and there are no immediate dangers and no side-effects.

Only two snags mar this therapeutic paradise. One concerns the difficulty of assessing dosage, for this has to be accurately adjusted for each patient if treatment is to be adequate and not too drastic (thus causing myxœdema). To this end two methods are used. By one method small, individually inadequate doses are given repeatedly until an effect is observed. By the other method an attempt is made, by estimating or guessing various factors in a complex equation, to achieve the desired result by a single dose. At the meeting most speakers seemed to favour the second method and produced evidence that it can be made to succeed; but further experience may yet disillusion them. On the other hand, the method of repeated small doses requires some means of acertaining rapidly the effect of the previous dose; otherwise treatment—already slower in action than either thyroidectomy or the antithyroid drugs—will be interminably prolonged. The effect of this treatment is difficult to assess by any means except clinically, for tests of radio-iodine uptake sometimes give misleading results after therapeutic doses—as indeed do such tests after surgical or drug treatment. The second snag concerns the possible long-term effects of intense irradiation. From what is known of the late effects of other forms of radiation on other tissues it seems possible that some patients treated in this way will eventually develop cancer of the thyroid. What will remain uncertain for at least another ten years is whether they will form an appreciable or an insignificant fraction of all the cases treated. For this reason all agreed at the meeting that radio-iodine should for the present be reserved for elderly thyrotoxics, except in special circumstances where other forms of therapy would be manifestly dangerous.

The treatment of established cancer of the thyroid with radio-iodine—described at the meeting by Dr. Pochin and by Prof. D. Waldron Smithers—is at once more disappointing and more exciting: disappointing, because so small a proportion of these cancers will concentrate iodine and so respond to treatment, and because the ones most readily treated (the most highly differentiated) are the ones which, in the absence of all therapy, often have a surprisingly good prognosis; exciting, because the isotopic method has great potentialities, if only its range can be increased. Already, thanks to work in America, the scope of radio-iodine has been extended a little further than at first seemed possible. Tumours which initially were extremely reluctant to concentrate radio-iodine have been induced to do so by removal of all normal tissue (otherwise too strong a competitor for the radio-iodine); and their concentrating power has then been further enhanced by the exhibition of thiouracil until a few days before the radio-iodine is given. But these tricks are not likely to succeed in papillary carcinomas, which unfortunately constitute the bulk of thyroid cancers; and it is still too early to say whether those tumours which respond favourably can ever be eradicated, rather than being merely held in check. So far notable successes are few, and failures numerous; but with inoperable cancer any success is important.

BORNHOLM AND COXSACKIE

SINCE Dalldorf and Sickles [1] first isolated a Coxsackie or "C" virus four years ago, members of this group have been found in the fæces and throat-washings of patients with various clinical conditions. One of these is epidemic myalgia or pleurodynia (Bornholm disease) in which there is strong evidence that these viruses are the ætiological agent. In the United States Curnen et al.[2] reported an epidemic of "aseptic meningitis" associated with "C" virus during which one patient infected with the same virus strain had the typical symptoms of Bornholm disease. They also noted that accidental infection of laboratory workers with this virus produced pleurodynia. Prompted by these findings, Weller and his associates [3] re-examined material from an outbreak of epidemic myalgia and isolated from it a similar serological type of Coxsackie virus. These viruses have also been isolated during epidemics in Europe and in this country.

The serological evidence, however, is still far from complete. Kraft and Melnick [4] have reported that in man the complement-fixation test may not be a reliable guide to recent infection with "C" viruses. Infection with one type of virus was found to initiate a rise in complement-fixing antibodies to both homologous and heterologous types. This is probably due to either a non-specific or an anamnestic reaction rather than to the presence of a common group antigen; and if this is so, other stimuli may induce a similar response, thus invalidating results based solely on the complement-fixation test. The neutralisation test does not seem to have this defect; for a rise only in homologous neutralising antibody has been found to follow infection. By this test Weller et al. demonstrated rising titres in the serum immediately after attacks of myalgia; and in this country Metcalfe Brown and his associates[5] have reported similar findings in two other cases during a typical epidemic. Lazarus et al.[6] also reported in two cases a rise of neutralising antibodies to the strain of "C" virus isolated during an epidemic of pleurodynia in Washington. In these outbreaks concurrent infection with "C" virus and Bornholm disease was demonstrated. In France, Lépine et al.[7] have isolated virus from muscle-biopsy material in two cases of this disease; this material also showed the characteristic histological changes noted in suckling mice infected with the virus. Thus direct evidence has been obtained that "C" virus is present at the site of the lesions, and is not a mere intestinal migrant fortuitously present in the patient.

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[9] Prakken, J. R. *Ibid.* 1952, 64, 87.

[1] Dalldorf, G., Sickles, G. M. *Science*, 1948, 108, 61.

[2] Curnen, E. C., Shaw, E. W., Melnick, J. L. *J. Amer. med. Ass.* 1949, 141, 894.

[3] Weller, T. H., Enders, J. F., Buckingham, M., Finn, J. J. *J. Immunol.* 1950, 65, 337.

[4] Kraft, L. M., Melnick, J. L. *Ibid.* 1952, 68, 297.

In poliomyelitis Coxsackie virus has been found together with the specific virus of that disease; but in epidemic myalgia there is no evidence that more than the Coxsackie virus is at work. It is now known that Bornholm disease is not due to one particular serological type of "C" virus; but the epidemic type of disease may be the manifestation of infection with the B rather than the A group of these viruses. (In suckling mice infection with group A causes diffuse myositis in skeletal muscle, while group B also gives rise to changes in fat and the central nervous system.) One type of virus, however, may produce epidemics in which the illness is predominantly either of the meningitic or of the myalgic type. Some variation was noted in the epidemics in Britain during last summer and autumn: in two there was severe and almost exclusive involvement of the abdominal and thoracic muscles, while in others the myalgia was more generalised and often associated with severe headache and occasionally with aseptic meningitis.

Because of the number of different strains in the group, the lack of a reliable in-vitro test, and the large numbers of suckling mice required for the neutralisation test, routine laboratory diagnosis of infection with this group of viruses is still out of the question.

PERIPHERAL NEURITIS

The problem of multiple peripheral neuritis or neuropathy remains a challenge to the clinician and the research-worker. In opening a discussion on this subject at the Royal Society of Medicine on April 3, Dr. J. St. C. Elkington mentioned that in a series of 34 cases of the disorder the ætiology remained obscure in 40%, and Dr. W. B. Matthews said that among 46 cases 70% were of uncertain ætiology. Some causes of peripheral neuritis have been recognised quite lately—for example, organic chemicals of various types, porphyria, amyloidosis, and carcinoma of the bronchus—but little is really known about the mechanism of the damage to the peripheral nerves, and the curious specificity of some poisons for certain parts of the nervous system remains unexplained. Dr. Elkington emphasised that morbid anatomy had given comparatively little information, and that biochemical studies were likely to prove the most fruitful line of investigation.

The biochemical aspect was dealt with by Prof. R. H. S. Thompson. One type of peripheral neuritis in which the biochemical mechanism is to some extent understood is that associated with thiamine deficiency, where, as a result of the lack of thiamine, carbohydrate metabolism in the nervous system cannot take place properly and pyruvate accumulates. The same breakdown in carbohydrate metabolism can, however, be brought about by other mechanisms. For example arsenic reacts with thiol groups in the protein molecules concerned in the pyruvate oxidase system,[1] and as a result in chronic [illegible] pyruvate accumulates. The clinical [illegible] arsenic polyneuritis and neuritic beriberi has long been recognised.[2] In a series of cases of polyneuritis of various types Thompson[3] estimated the blood-pyruvate levels after a loading dose of glucose; and he has tentatively divided this disorder into three biochemical types. In the first group the blood-pyruvate level following ingestion of glucose is raised, but after a course of treatment with large parenteral doses of thiamine the pyruvate levels return to normal; in this group it seems that the peripheral neuritis is associated with breakdown of carbohydrate metabolism due to dietary or conditioned thiamine deficiency. In the second group the blood-pyruvate level also rises after glucose ingestion; but the levels do not return to normal after massive doses of thiamine, and in these cases it is possible that the enzyme system is damaged by some toxin, either endogenous or exogenous, acting in a manner comparable to that in which arsenic acts. Professor Thompson suggested that treatment with dimercaprol should be tried in this group of cases, but in the few cases where it had been used so far the benefit had not been striking, although Furmanski[4] had reported improvement in four cases in which blood-pyruvate levels had not been estimated. In the third group the blood-pyruvate levels are normal even after ingestion of glucose, and probably there is no disturbance of the enzyme system concerned in carbohydrate metabolism in the nervous system.

One chemical poison known to cause peripheral neuritis together with changes in the white matter of the spinal cord is tri-*ortho*-cresyl phosphate, the substance concerned in the celebrated outbreak from the drinking of adulterated Jamaica ginger extract in the United States in 1930.[5] [6] This substance has also caused peripheral neuritis when it has adulterated cooking-oil.[7] Thompson has found that in vitro it inhibits the action of pseudo-cholinesterase—an enzyme present in the blood-serum, the peripheral nerves, and the white matter of the spinal cord, and distinct from the true cholinesterase present at the motor end-plates. Limited in-vivo experiments on chickens seem to have confirmed this action of tri-*ortho*-cresyl phosphate. The physiological activity of pseudo-cholinesterase remains something of a mystery, but these findings suggest that biochemical studies may clarify the mechanism of another type of peripheral neuritis. A further promising line of research may be closer study of the blood-supply of the peripheral nerves, as peripheral neuritis is sometimes associated with recognised disorders of the blood-vessels, such as polyarteritis nodosa and systemic lupus erythematosus.[8] A possible bridge between the two mechanisms is the hyperplastic fibrosis of the smaller arteries and capillaries of the spinal cord, the peripheral nerves, and the muscles in polyneuritis due to tri-*ortho*-cresyl phosphate.[5]

On April 7 Sir Russell Brain was re-elected president of the Royal College of Physicians of London.

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[5] Metcalfe Brown, C., Liddle, D. C., Tobin, J. O'H. *Lancet*, March 1, 1952, p. 445.

[6] Lazarus, A. S., Johnston, E. A., Galbraith, J. E. *Amer. J. publ. Hlth*, 1952, **42**, 20.

[7] Lépine, P., Desse, G., Sautter, V. *Bull. Acad. Méd. Paris*, 1952, **136**, 66.

[1] Peters, R. A., Sinclair, H. M., Thompson, R. H. S. *Biochem. J.* 1946, **40**, 516.

[2] Ross, R., Reynolds, E. S. *Brit. med. J.* 1901, ii, 979.

[3] Joiner, C. L., McArdle, B., Thompson, R. H. S. *Brain*, 1950, **73**, 431.

[4] Furmanski, A. R. *Arch. Neurol. Psychiat.* 1948, **60**, 270.

[5] Aring, C. D. *Ibid*, 1942, **65**, 34.

[6] Smith, M. I., Elvone, E., Frazier, W. *Publ. Hlth Rep., Wash.* 1930, **45**, 2509.

[7] Hotston, R. D. *Lancet*, 1946, i, 116.

[8] Heptinstall, R. H., Sowry, G. S. C. *Brit. med. J.* March 8, 1952, p. 525.

Special Articles

CROSS-INFECTION IN HOSPITAL WARDS

ITS INCIDENCE AND PREVENTION

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LATELY MEMBER OF TEAM INVESTIGATING FUNCTIONS AND DESIGN OF HOSPITALS (NUFFIELD PROVINCIAL HOSPITALS TRUST AND THE UNIVERSITY OF BRISTOL)

CROSS-INFECTION is a matter of considerable importance to hospital planners. Sir Wilson Jameson in 1944 reminded hospital committees and administrators that "cross-infection is a steady drain on the hospital purse and efficiency," and he recommended that, "when building is contemplated, the prevention of cross-infection should be an overriding consideration, and expert advice should be sought" (Medical Research Council 1944).

In a report to the British Pædiatric Association (1946) an ad hoc committee remarked: "Whilst a good deal has been written about cross-infection in children's wards, the frequency, extent, and results of this have never been ascertained." Watkins and Lewis-Faning 1949) reported the results of an investigation into the ncidence of cross-infection in children's wards, in which 14 hospitals and 26 wards coöperated. They found an over-all incidence of cross-infection of 7·1% after surveyng 9619 children for 11 months. I am unaware of any other research of a similar kind, and none seems to have been undertaken in adult wards.

I have approached the problem of cross-infection in wo ways: by enlisting the help of hospital staffs in keeping records of infections in their wards over varying periods; and by examining the wards where records were being kept, in order to understand the circumstances of cross-infection, and the methods employed to prevent t. I have tried to obtain information on the relative mportance of cross-infection in many different types of ward, and a special effort has been made to confirm each infection bacteriologically as far as possible. A knowedge of the frequency with which particular organisms are responsible might enable us to advise hospital planners on the relative importance of, for example, dust, droplet nuclei, and human contact, in the spread of nfections, and in their prevention.

Incidence of Cross-infection

RECORDING OF CASES

Specialists in 8 hospitals agreed to keep records of all infection in their wards over a period of six to twelve months. Records were not confined to those infections considered to be cross-infections, and they also included those present or incubating on admission. No attempt, however, was to be made to record cross-infections which did not give rise to clinical symptoms.

Cross-infection has been defined as:

> ". . . any infection acquired by a patient in the hospital environment. Clinically it is an infection arising during the course of another illness for which the patient was originally admitted to hospital, and may attack the respiratory tract, gastro-intestinal tract, wound, skin, or mucous membrane, or be manifested as one of the specific fevers" (British Pædiatric Association 1946).

According to this definition all the infections recorded, other than those from which patients were already suffering or which they were incubating at the time of admission to hospital, would be cross-infections.

A separate note was made of infections in the staffs of each ward, and in some instances, of the operating-theatre and labour ward.

Two forms were designed, one for the patients and one for the staffs. The information asked for was extensive, and for patients it included: (1) Diagnosis on admission. (2) Any infection present, or later found to have been incubating, at the time of admission. (3) A monthly record of all infections giving the nature and duration of each. (4) Disposal of the patient. (5) Follow-up notes. (6) The clinician's opinion on the source of the infection, and his estimate of any additional time in hospital which it necessitated. (7) *Bacteriological* confirmation of all infections as far as possible.

FINDINGS

Records were received from 13 wards in the 8 hospitals, covering 5095 patients under care during the year 1950. Some results are set out in the accompanying table.

Ward Staffs

In 4 wards records were kept of staff illness for ten months, 2 children's wards kept staff records for 6 months, and two further records (surgical and medical) were kept respectively for two and seven months. The staff surveyed were mainly nurses, but the total of 223 included 45 doctors. Colds accounted for approximately 60% of all their illnesses. Sore throats and minor septic conditions, such as a septic finger or boil, accounted for a large proportion of the remainder, and gastro-enteritis, impetigo, and otitis media were not infrequent.

In cases which were confirmed bacteriologically, the chief organisms isolated were *Staphylococcus aureus*, *Staph. albus*, *Streptococcus pyogenes* (group A), and *Strep. pneumoniæ*.

Patients

The over-all incidence of infection for all types of ward, irrespective of the time for which the records were kept was 9·9%. For the 4 wards (2 surgical and 2 maternity) covering the same ten months, the incidence of ward infection was 9·5%.

Some points of interest in the table are:

The highest rate of infection was 21% in a children's ward. This ward was specially selected because it was very old and badly constructed, with few amenities. The other children's ward had no cubicles, but it was spacious and well ventilated; here the incidence of infection was 15%.

The 3 maternity wards had a relatively low infection rate (5–6%); a general surgical ward had the lowest figure of all (3%), but, since the records cover only two months, the result is less reliable than those for other wards.

Wards for special types of surgery had rather a high rate —namely, neurosurgery 19%, plastic surgery 18%, and thoracic surgery 15%.

Types of Infection

Children's wards.—The common cold was the most frequent infection and upper respiratory infections came second. Whooping-cough and conjunctivitis were common in 1 ward. The remaining infections were varied—i.e., pneumonia, mumps, boils, otitis media, infective hepatitis, and urinary infections.

The organisms most often isolated were *Staph. aureus* (coagulase-positive, penicillin and streptomycin resistant) and a hæmolytic streptococcus, usually of group A. Both organisms were found commonly in throat and nose infections, and occasionally in boils and otitis media.

Maternity wards.—Urinary infections and puerperal infections were seen most often, and phlebitis and mastitis came next. Among the babies impetigo and conjunctivitis were the most numerous, with an occasional outbreak of pemphigus, thrush, and the common cold.

In 1 ward *Bact. coli* was isolated in most urinary infections, and *Staph. aureus* in all cases of impetigo. In puerperal infections *Staph. aureus*, *Strep. fæcalis*, and a hæmolytic streptococcus were found. In the other ward *Staph. aureus* was found in impetigo, pemphigus, and puerperal sepsis, *Staph. albus* in puerperal sepsis and cystitis, and in some cases *Strep. fæcalis* and a hæmolytic streptococcus.

Surgical wards.—Wound infections were comparatively frequent, followed by colds and respiratory infections. Other troubles in the 3 general surgical wards were urinary infections, abscesses, phlebitis, and cellulitis.

In 1 ward 7 patients suffered from phlebitis following injections, and in another there were 3 cases of salmonella infection. Infective hepatitis, peritonitis, otitis media, and sinusitis, accounted for most of the remaining infections.

In 1 ward *Staph. aureus* was the commonest organism isolated, followed closely by a hæmolytic streptococcus and *Proteus vulgaris*. *Bact. coli*, *Staph. albus*, diphtheroids, pneumococci, and *Pseudomonas pyocyanea* were obtained in a few cases. In 2 general surgical wards of another hospital, *Staph. aureus* accounted for many infections. In all 3 wards this staphylococcus was frequently coagulase-positive, and resistant to sulphonamides, penicillin, and streptomycin.

Medical ward.—Only 1 medical ward was studied, and the patients in it were mainly elderly chronic invalids. The common cold, sore throats, and conjunctivitis formed the greater part of the infections; the remainder were pneumonia, abscesses, and urinary infections.

In a few cases a coagulase-positive *Staph. aureus* was isolated; other organisms included a hæmolytic streptococcus, *Bact. coli*, and *Bact. fæcalis-alkaligenes*.

Special wards.—In the 3 special wards (neurosurgery, plastic surgery, and thoracic surgery) infected wounds accounted for a high percentage of infections. Pneumonia and other respiratory infections were also prominent.

Staph. aureus was again by far the commonest organism isolated, with *Staph. albus* second. Other organisms found were *Proteus vulgaris*, a hæmolytic streptococcus, *Strep. viridans*, anaerobic streptococci, *Bact. coli*, and *Ps. pyocyanea*.

DELAY IN DISCHARGE

In 3 surgical wards it was estimated that 40 patients out of 851 had to stay longer in hospital because of

ANALYSIS OF INFECTIONS RECORDED IN 13 WARDS

Type of ward	No. of beds	Average age of patients (years)	No. of patients surveyed	Average length of stay in ward	Period of survey	% of patients who developed infection	Analysis of types of infection expressed as % of total	Principal organisms isolated	Estimated average delay in discharge caused by infection
General surgery (female)	28	13	84	29 days	2 mos.	3 %	Too few to analyse	*Ps. pyocyanea*	..
General surgery (female)	32	16	250	14 ,,	5 ,,	12 %	Infected wounds (58 %) Colds and upper respiratory infections (17 %) Urinary infections (14 %)	*Staph. aureus* *Bact. coli* Hæmolytic streptococcus Pneumococci *Proteus vulgaris* *Ps. pyocyanea* *Staph. albus*	19 days
General surgery (female)	30	47	474	24 ,,	10 ,,	12 %	Wound infections (46 %) Colds and upper respiratory infections (30 %) Urinary infections (9 %) Abscesses, boils, cellulitis (3 %)	*Staph. aureus* *Proteus vulgaris* *Bact. coli* *Strep. fæcalis*	13 ,,
General surgery (male)	30	43	476	28 ,,	10 ,,	15 %	Wound infections (47 %) Urinary infections (4 %) Colds and upper respiratory infections (14 %) Phlebitis (10 %) Abscesses, boils, cellulitis (10 %)	*Staph. aureus* *Ps. pyocyanea* *Proteus vulgaris* Various streptococci	50 ,,
Maternity ..	40	27 (mothers)	300	4 ,,	3 ,,	5 %	Urinary infections (26 %) Infected wounds and perineum (20 %) Phlebitis (13 %)	Enterococci in 3 cases	10 ,,
Maternity ..	21	26 (mothers)	1210	11 ,,	10 ,,	6 %	Puerperal sepsis (42 %) Urinary infections (30 %) Mastitis (4 %) Babies { Impetigo (12 %) Babies { Conjunctivitis (7 %)	*Staph. aureus* *Strep. fæcalis* Hæmolytic streptococcus *Staph. albus* *Bact. coli*	3 ,,
Maternity ..	21	28 (mothers)	1411	12 ,,	10 ,,	5 %	Urinary infections (32 %) Puerperal sepsis (27 %) Babies { Impetigo (19 %) Babies { Ophthalmia (4 %)	*Staph. aureus* *Ps. pyocyanea* *Strep. fæcalis* *Staph. albus*	3 ,,
Medical (chronic)	52	70	98	4¼ years	7 ,,	11 %	Colds (36 %) Conjunctivitis (18 %) Sore throats (tonsillitis) (18 %)	*Staph. aureus* Hæmolytic streptococcus *Bact. fæcalis-alkaligines* *Bact. coli*	6 ,,
Neurosurgery ..	25	41	64	20 days	2 ,,	19 %	Infected wounds (32 %) Pneumonia (32 %)	*Staph. aureus* *Staph. albus*	..
Plastic surgery ..	30	29	273	33 ,,	5 ,,	18 %	Infected skin grafts (55 %) Colds and upper respiratory infections (18 %) Infected wounds (18 %)	*Staph. aureus* Hæmolytic streptococcus *Staph. albus* *Proteus vulgaris* *Ps. pyocyanea*	18 ,,
Thoracic surgery	45	45	139	Not recorded	3 ,,	15 %	Infected wounds (57 %) Pneumonia and respiratory infections (33 %)	*Staph. aureus* Hæmolytic streptococcus *Proteus vulgaris* *Strep. viridans*	60 ,,
Children ..	26	4¾	181	17 days	6 ,,	21 %	Colds (49 %) Tonsillitis and upper respiratory infections (13 %) Conjunctivitis (10 %) Whooping-cough (8 %)	*Staph. aureus* Hæmolytic streptococcus Pneumococci *Bact. coli*	..
Children ..	15	4	134	16 ,,	6 ,,	15 %	Colds (60 %) Tonsillitis and upper respiratory infections (14 %)	Hæmolytic streptococcus *Staph. aureus* Pneumococci *Salmonella typhimurium*	28 ,,

acquired infection. The estimated average increase per infected patient was twenty-one days. In one of the maternity wards the increase was ten days per affected patient, but in the 2 others it was estimated at only three days. In the thoracic ward the estimated increase was as high as sixty days.

These estimates do not, of course, include those patients who, in the opinion of the clinician, did not have their stay in hospital prolonged by infection. In no instance was a death attributed to infection acquired in the ward.

Observations in the Wards

I was able to study 24 wards in 13 hospitals, including the 13 wards where infections were analysed; there were 10 general surgical wards, 4 medical, 3 maternity, and 2 children's, and also 1 each for ear, nose, and throat surgery, neurosurgery, thoracic surgery, plastic surgery, and a neurological unit. I was accompanied in each case by the ward sister or her representative, but my visits were often long and I was sometimes allowed to interest myself in the wards for short periods unescorted.

PLANNING OF WARDS

Most wards were of the large, open type with 18–25 beds arranged at right angles to the walls. The older wards were long and narrow, while the newer ones tended to be more square and had much more space in the centre. Some had been partitioned, but the majority were undivided. Side wards with a single bed were provided in more than half and some wards were split into a series of small rooms, containing from 1 to 8 beds. The distance between the adjacent sides of beds in one ward varied between 22 in. and 65 in. Other measurements showed that, while the average space between the centres of beds was about 7 ft., big variations were common. A separation of 8 ft. has been recommended (Medical Research Council 1944).

Almost all wards depended on large windows for cross-ventilation, but there was no consistent policy towards opening or shutting windows. Even during the dressing of wounds some shut their windows and others left them open.

The Medical Research Council (1944) stated that "the large, open ward must be considered as obsolete . . . subdivision into smaller units . . . should be encouraged and undertaken as opportunity arises." The newer wards which I visited were usually subdivided, but it was disappointing to find that nearly half the wards had no single rooms. In neither of the 2 children's wards were there single rooms, though in 1 there were wooden partitions between cots. The Medical Research Council (1944) recommended that "nearly half the number of beds in a children's or an infectious diseases' hospital should be in individual cells." Other authorities in favour of single rooms for children include Spence (1947), the British Pædiatric Association (1946), and the Department of Health for Scotland (1947).

PEOPLE IN THE WARDS

Nursing Staff

It is generally agreed that a sufficiency of trained staff is an important factor in the control of cross-infection. For infants 2 nurses to 3 cots has been recommended as a minimum (Department of Health for Scotland 1947); and in a children's ward of 20 beds "there should be at least 2 trained staff nurses for day duty and 2 for night duty, and the total number of nurses should approximate 1 per patient for the twenty-four hours" (British Pædiatric Association 1946).

Of the 2 children's wards, 1 had 26 cots and beds and 10 nurses, of whom 3 were fully trained; and in the other ward of 20 cots and beds there were also 10 nurses but only 2 were fully trained. The largest nursing staff was found in a thoracic surgery unit which had 26 nurses (11 fully trained) for 36 beds and 9 patients who lived out, and the smallest staff was found in a plastic surgery unit of 30 beds with 6 nurses (3 fully trained).

Nurses were not always provided with adequate means of washing their hands; 1 ward had no wash-basins at all, and, in order to wash, the nurses had to go into the sister's office. Usually, but not always, there were one or two wash-basins, with running hot and cold water. In 1 ward enamel basins were used which had to be filled and emptied in the ward kitchen.

I inquired about the maintenance of health among nurses. Almost all the ward nurses were immunised against diphtheria and vaccinated against smallpox, and B.C.G. inoculations and X-ray examinations of the chest were often given to new entrants.

There was a very striking similarity in the procedure adopted when one of the nurses fell sick. When a nurse feels ill, she reports to the ward sister who takes her to matron's office where she is seen either by matron or one of the nursing superintendents: thence she is sent or taken to the home sister. If she is sufficiently ill she is put to bed in the nurses' sick bay and either a registrar, the medical superintendent, or one of the consulting staff comes to see her. Sometimes she is taken to the outpatient department and seen by one of the consultants there. There is often a definite morning "sick parade" for nurses at about 7.30 A.M.

Medical Staff

I found it difficult to obtain reliable information on the state of health and habits of the medical staff. If a doctor is unwell, whether with a cold or anything else, he is a law unto himself. Generally he continues to do his ward rounds.

The number of doctors who attended patients in wards was often considerable; in a children's ward with 20 patients, 15 doctors were on the ward staff. On the other hand, the medical ward for chronic invalids had 2 doctors for 52 patients. The average ratio in 16 wards was 1 doctor to 8 patients.

Domestic Staff

A typical domestic staff consisted of 1 full-time ward-maid and 2 "daily women." Their duties were mainly scrubbing floors, cleaning lockers and sluices, and washing dishes. In several wards they helped to serve food and occasionally cut bread.

When one of the domestic staff fell ill it was usual for her to attend her own doctor, but in an emergency she was treated at the hospital.

No courses of instruction in elementary hygiene were held in any of the hospitals (Central Health Services Council 1950).

Cloakrooms for the domestic staff were badly needed: I found their hats and coats in passages, bathrooms, kitchens, and linen cupboards; often too, there was also no proper place for nurses' cloaks. In one ward I visited they hung over the dirty linen bins in the sluice-room.

Crockery and Utensils

Only 1 ward had a modern sink unit for washing up. Here the crockery and utensils were first washed in water containing a detergent and then rinsed in a second sink. Finally they were sterilised by boiling water. The hot crockery dried so quickly in racks that it was not necessary to use a cloth.

In almost all wards crockery was washed in one sink—a thoroughly unsatisfactory method. Higgins and Hobbs (1950) compared the bacteriological counts obtained from crockery and utensils in 20 restaurants and canteens. The only satisfactory washing system was shown to be that using hot-water sterilisation. "Enormous numbers of coliform bacilli and staphylococci were counted on cups, plates, spoons, and forks in the one-sink kitchens. The drying towel was heavily contaminated in almost every case."

Visitors

It was theoretically possible for visitors to enter almost any ward in an infectious condition. Ward sisters would sometimes examine and occasionally turn back visitors who had obvious infections, but this protection was very superficial. One sister said that she obtained information about expected visitors from the patients themselves, and could occasionally give advice on the suitability, for example, of a visit from a known tuberculous individual.

In a children's ward all visitors were required to wear masks, but in most other wards masks were not insisted upon. Maternity and childrens' wards did not usually allow children to visit patients. The diversity of the regulations for visitors was very noticeable.

TREATMENT ROOMS AND DRESSING OF WOUNDS

Special treatment rooms where wound dressings and other procedures could be carried out in relatively sterile surroundings have repeatedly been advocated. (Bourdillon and Colebrook 1946, Spence 1947, British Pædiatric Association 1946.) Only 2 of the wards visited had treatment rooms and in neither was there controlled ventilation. 2 wards carried out all dressings in the nearby surgical theatres, but all the remaining wards dealt with wound dressings in the ward. A very definite attempt was made in most wards to avoid bedmaking or any form of dust raising for half to one hour before dressings were changed. On the other hand, windows were sometimes left open.

The "no touch" technique (Medical Research Council 1941) was adopted in all the wards. I saw a number of dressings being done and the technique was very good. However, some wards were unable to spare 2 nurses at a time for dressings and a single nurse in a hurry was unable to carry out the same technique. Ward sisters told me that sickness, time off, and tutorials were the main reasons why 2 nurses could not always be provided for dressings. A technique for changing wound dressings which can be carried out by 1 nurse has been described (Central Health Services Council 1950).

One item which could be improved was the bin into which the dirty dressings were put. Only a small minority of wards had bins with lids and foot pedals; a bin with a lid which had to be removed by hand was more usual, and even a flat tray covered with newspaper was sometimes used. In a ward of a teaching hospital the surgeon had provided suitable bins at his own expense.

TOILET ARRANGEMENTS

Each of the 24 wards had at least one bathroom and one W.C. for the use of patients. They often opened off the sluice-room, through which patients had to walk to use either the bath or W.C. From the economic point of view this arrangement was probably sound enough, but in practice it was a great inconvenience to both patients and nurses. I noted the number of baths provided in each of 19 wards; the most generous provision was one bath for 12 patients, and the most meagre was one bath for 33 patients. The number of W.C.s varied from one for every 9 patients to one for every 24.

All the ward bathrooms, with one exception, were used for many purposes other than bathing patients. For example, mackintoshes were often carbolised in the bath and hung up to dry. Some wards had slabs in the sluice-room for this purpose but many had not. A surgical ward had no suitable means of sterilising bedpans, and each evening they were filled with 'Lysol' and left in the bath for some hours. I saw a number of bathrooms in which pillows, oxygen cylinders, dirty-linen bins, urine-testing apparatus, wet bandages, and the outdoor clothes of the domestic staff were occupying a great deal of space. It was a common "dumping ground" for trolleys or any odd article, such as a dispensary basket or ultraviolet lamp, for which no other convenient place could be found. In some very old types of ward the sluice-room and bathroom were one and the same, and in one comparatively modern room, built in 1949, the bath was in the centre of what might best be described as a clean utility room, where sinks were provided for washing bowls and instruments, and where sterilising was carried out.

The bathroom was often the first room which a new patient entered. Unconscious or severely ill patients were normally bed-bathed in the ward, but otherwise new patients were sent to undress and bath themselves, or be bathed, in the bathroom. One ward sister said that in her experience patients bathed at home and put on clean underclothes before arriving at the ward for admission, and therefore it was exceptional for most of her patients to be bathed on arrival.

Many wards insisted on one bath a week for each patient and in some I was told that a patient could have as many baths as he wanted. A bath-book which included a note on the state of skin, nails, and hair, was often kept by ward sisters as a precaution against pediculosis and other skin troubles. Generally a nurse entered these particulars in the bathroom and she was also responsible for the cleaning of the bath, though this was sometimes done by the patients themselves. This process was, of necessity, perfunctory and the real cleaning was done once or twice daily by a nursing orderly with 'Vim,' 'Dettol,' or phenol. Baths are very difficult to sterilise and under the circumstances I have described it must have been possible for infection to spread from patient to patient.

The impression I gained after seeing these bathrooms and the many uses to which they were put, was that there were too few baths and no incentive to the more fastidious to make use of those available. Bathrooms were put to many uses because of lack of storage space in the ward annexes. Obviously there should be more baths, and they should be reserved for their proper purpose.

SLUICE-ROOMS

The design of most sluice-rooms was a muddle. Clean and dirty work went on side by side; sterilisation, the storage of dirty linen and dressings, and the disposal of excreta were sometimes carried out in the same room. Bathrooms and W.C.s were commonly partitioned off in the same area, and the total space available was incredibly small—e.g., 9 ft. by 12 ft. for a sluice-room serving 30 patients. A typical provision was 1 sluice-room to 25 patients, but 1 to 10 and 1 to 36 were the extremes.

In one sluice-room the following articles were stored: bedpans, washbowls, tooth-mugs, sputum-mugs, dirty linen, dirty-dressing bins, dressing trolleys, and toilet trolleys. Other common findings were flowers, mackintoshes, urine-testing apparatus, hot-water bottles, enema trays, brooms, and clothing. The more permanent fixtures included the sluice itself, sinks, porcelain slabs, shelves, cupboards, and in some cases sterilisers. In one sluice-room the floor was largely covered with containers called "urine hats," and, while the usual work of a sluice-room proceeded, patients wended their way through the "urine hats" to the bath and the W.C.s, which were partitioned off in the same room.

The outstanding defects were the lack of space, the mixture of clean and dirty functions, the association of patients' baths and W.C.s, and the general congestion.

DISPOSAL OF DIRTY DRESSINGS AND SOILED LINEN

A fairly uniform system of disposal of dirty dressings was in operation in most wards. Usually there were at least two bins with lids in the sluice-room or bathroom. One bin was kept for dry dressings and the other for wet dressings; the wet-dressing bin usually contained an antiseptic solution. These bins and the dirty-linen container had often to be carried the length of the ward to be emptied. Porters usually called once or twice a day with a larger bin on wheels into which the contents of the ward bins were emptied. In a few wards a nurse carried the bin down to the basement where she emptied it into a larger bin whose contents were then incinerated. The final disposal was always incineration.

Almost half the wards still counted their soiled linen. The linen was usually changed in the morning when beds were made. The soiled linen was then taken to the sluice-room or bathroom and stuffed into either a bin with a lid or a soiled linen bag of the type recommended by the Medical Research Council (1944). Later in the day a junior nurse pulled all the soiled linen out of the bin or bag, arranged the various articles in pile on the floor, and counted them. She then stuffed them back into the container to await removal by a porter. Sometimes there was so much soiled linen that it was impossible to close the lid or the top of the bag. Most wards rinsed grossly contaminated articles in the sluice-room sink before sending them to the laundry, which would not accept them otherwise. Some wards not only counted linen "out" but "in" as well, and in one instance, after a ward count, a nurse took the linen to the supervisor where it was checked and counted again.

An annotation in *The Lancet* (1949) says:

> "Some antique practices in the handling of soiled linen persist in many of our hospitals. It is customary for nurses, before sending linen down to the laundry, to count and sort it in the ward, and to "sluice," or rinse out, badly soiled articles in the sluice room—or even in the ward bathroom. The laundry maids count the linen again, both before and after washing it, and the nurses count it once more when it gets back to the ward. The whole elaborate process is not only time-consuming but unhygienic and even at times dangerous."

The annotation then describes how in the London Hospital the soiled linen goes straight from the bedside into sacks which are dropped down a chute to the basement where an electric trolley carries them to the laundry uncounted. At the present time fouled linen at the London Hospital is put into a separate bag, distinctly coloured green, before being added to the merely soiled linen in the sack. A machine in the hospital's laundry is reserved for washing foul linen, and the contents of the green bags can be tipped straight into it without further handling.

DUST SUPPRESSION

Much evidence has been produced to show that dust suppression is necessary (Garrod 1944) and that it can be achieved by incorporating oil in bed-linen, blankets, towels, gowns, &c. (Rountree 1947), and by treating ward floors with spindle oil (van den Ende et al. 1940). Almost all the published recommendations on the prevention of cross-infection in hospitals include the oiling of bedclothes and floors (Medical Research Council 1941, 1944, 1948, British Pædiatric Association 1946). It was, therefore, surprising that none of the 24 wards oiled either bedclothes or floors.

The reason was not always obvious. The oiling of floors had been abandoned in a few wards because the slippery surface and the damage to rubber soles of shoes and tyres on ward furniture made it unpopular. An objection to the oiling of bedclothes was that a washing-machine must be set aside for the purpose, with staff to mind it. In 14 wards the floors were made of wood and in 3 they were covered with linoleum; so the majority were suitable for oiling.

The commonest practice in the wards was to dry-sweep the floor with a broom two or three times a day. A ward sister told me that she put down tea-leaves before sweeping, but nowhere else was it customary to damp the floor. Floors were generally scrubbed with soap and water every three months, and polishing daily with a "dummy" was usual; sometimes an electric polisher was used, but very few wards possessed any form of vacuum cleaner. In none was there a built-in vacuum pipe as recommended by Bourdillon (1948).

FOOD AND MILK

Food was always prepared in a central kitchen and sent to the wards for distribution. Patients had individual trays in 1 ward, but this method was considered wasteful. Refrigerators, as well as storing milk and butter, were commonly used for penicillin, blood, and skin or cartilage, depending on the kind of ward. Sometimes pathological specimens stayed in the refrigerator pending transfer to the laboratory.

Milk was usually delivered in bottles, but about a third of the wards received their milk in cans, which were cleaned in the wards. They were simply washed in warm water with a dish cloth and sometimes cleaned again in the central kitchen. Some milk was certified as free from tubercle bacilli, other supplies were not; it was not the custom in any ward to boil the milk.

MASKS

The Medical Research Council (1944) recommended face masks consisting of six layers of 40-mesh gauze or two layers of gauze with an impermeable 'Cellophane' or paper insert.

I was shown a great variety of masks during my visits. In 5 wards I was told that masks were never worn; these wards included an acute surgical ward in which a fair number of wound dressings were performed. The surgeon, I was told, "did not believe in masks." Often several layers of gauze in the form of a bandage were used to cover the mouth and part of the nose, and the gauze was discarded after use. A single layer of linen was used in 1 ward; there was a slit for the eyes and the linen mask covered the face and entire head. In 2 wards muslin masks fitted with an impervious layer were in use.

Masks were worn while changing dressings and swabbing, and while attending infants. In 1 maternity ward masks were used almost all the time. In some wards it was customary to wear masks for catheterisation, blood-transfusions, and the setting up of saline drips, as well as when dealing with infectious cases.

THERMOMETERS

Green and Penfold (1947) and Albury (1947) have drawn attention to clinical thermometers as a possible source of cross-infection. They recommended that every patient should be provided with his own thermometer during his stay in hospital. The Medical Research Council (1944) also encouraged the use of individual thermometers and advised that they should be kept in liq. borac. et formaldehyde (*N.W.F.*). Court (1949) preferred a 1 in 60 solution of phenol.

Only 3 of the wards provided a thermometer for each patient, and in 16 wards the average was one thermometer to 6 patients. A ward of 32 patients was provided with only two thermometers. The following disinfectants were used: Biniodide of mercury (1 in 1000), 'Glyco-thymoline,' methylated spirit, dettol, phenol (in varying strengths), and 'Milton.'

It was usual to change the disinfectant once a week, but a few wards changed it daily and some every fourteen days—or when someone remembered.

STERILISATION METHODS

Towels, Dressings, and Gloves

In every ward towels, dressings, and gloves were sterilised in an autoclave; the majority sent these articles to one of the operating-theatres. It was not always convenient for me to see the process when the theatre was in use, and when the autoclave was in the care of a technician or male orderly he was a difficult person to find. Some of the autoclaves which I did see were extremely old—usually the ones found in the basement and operated by a porter.

Towels and dressings commonly received twenty minutes' treatment with steam at 20–25 lb. pressure, after which they dried for twenty to thirty minutes in hot sterile air. Gloves had ten minutes' treatment with steam at 10–15 lb. pressure and ten minutes drying. No mention of temperature was generally made, and I presume that this was about 120°C. In a few hospitals, the autoclave was supervised by a bacteriologist (Medical Research Council 1941), but usually the theatre sister or the porter was in sole charge.

Bowls and Instruments

The Medical Research Council (1941) recommended that bowls and instruments should be sterilised by total immersion in boiling water or soda solution for two minutes, and should be protected from dust by sterilised lids. Disinfectant solutions were not advised.

The custom in the wards which I visited was rather different. Almost every ward boiled bowls and instruments for twenty minutes; 2 wards thought three minutes was long enough; and 1 ward boiled their bowls for two hours and their instruments for thirty minutes. In many wards, however, sharp instruments, especially scissors, were kept in spirit, lysol, or dettol, and rinsed before use in saline or sterile water. Sometimes the saline or "sterile" water was freshly prepared in small quantities, but on occasions a large Winchester bottle was provided to last for a fortnight or more.

Syringes

Sterilisation of syringes is best performed in an autoclave or a hot-air oven, and failing these by boiling in water (Medical Research Council 1945). Syringes should not be wrapped in lint before boiling, because the lint may prevent the syringe from reaching the temperature of the water. Syringes should be boiled in water for five minutes and allowed to dry before use. The only chemical disinfectant recommended was 70–75% alcohol; spirit was not advised. Only syringes made entirely of glass should be sterilised in alcohol, and they should be immersed for five minutes. This process will kill all vegetative bacteria but not spores, and syringes so sterilised should be used only for the injection of sterile fluids such as insulin. All syringes used for aspiration and venepuncture should be sterilised by heat. A central syringe service in the charge of a specially trained sister was also advocated, whereby syringes are sterilised in a hot-air oven in the laboratory under the supervision of a pathologist. Here I again found that the recommendations were not always carried out. Only 2 wards received syringes from a central sterilisation service and 3 wards in other hospitals had syringes autoclaved in the operating-theatre. The dispensary supplied dry sterile syringes to a few wards, but in most cases they were sterilised in the ward by boiling. The commonest procedure was to keep the syringes in spirit and rinse them with sterile water before use. They were usually boiled after use and then put back in spirit until required again. Most wards kept a hypodermic syringe in spirit for injections of morphine or other drugs, and these syringes were sometimes "used out of spirit" and not boiled. Syringes for penicillin were often kept separately and were dry-sterilised. Needles were boiled for twenty minutes, and if more than one injection had to be made the needle was changed but not always the syringe—a practice not without risk (Evans and Spooner 1950).

Bedpans

There is some doubt whether the sterilisation of bedpans after use is always necessary.

The Medical Research Council (1944) advises disinfection after every use, preferably by heat. When this is impossible immersion in a 1 in 80 solution of a general disinfectant for at least one hour is recommended (Central Health Services Council 1950).

In 3 wards bedpans were sterilised by steam for three minutes in special combined bedpan washers and sterilisers, and 2 wards boiled their bedpans once daily in large sterilisers. No other wards sterilised bedpans, the usual routine was to disinfect them with 1 in 20 lysol or phenol once daily.

Sputum-mugs

These mugs should be boiled for two to five minutes and sputum should be disinfected before it is disposed of (Medical Research Council 1944). I found that the contents of sputum-mugs were usually emptied down the sluice without being disinfected; the mugs were then cleaned in the sink, and generally boiled for twenty minutes, but a fair number of wards did not boil them. Disinfectant, such as phenol, was sometimes left in the bottom of mugs before issuing them to patients, but in 1 ward this was stopped because "the patients drink the disinfectant" by mistake. None of the wards used the waxed paper sputum-mugs now obtainable, which are translucent and graduated in fluid ounces for measuring the amount of secretion, have screw-on lids, and are destroyed after used.

Conclusions and Summary

Information about cross-infection was collected from 13 wards in 8 hospitals, covering periods up to ten months. Of 5095 patients, 9·9% developed an illness defined as cross-infection.

The commonest troubles were colds and upper respiratory infections, wound infections, urinary infections, and minor septic conditions. The organism most frequently isolated was *Staph. aureus*.

Personal observations in 24 wards showed that the means adopted in many wards to prevent cross-infection were unsatisfactory, and many published recommendations were not being tried.

There is need for a committee (such as exists in some hospitals) to supervise and coördinate the prevention of cross-infection.

Ward sisters would benefit from refresher courses in preventive measures at intervals of, say, three to five years. Alternatively, they should not stay too long in one ward lest their methods become too rigid.

In planning wards and their annexes much more attention should be paid to the requirements of the nursing staff. The separation of clean and dirty sluice-room accommodation and the provision of more baths, w.c.s, wash-basins, cloakrooms, and storage space are essential.

Certain practices such as the counting of dirty linen by nurses, the dry-sweeping of floors, and the keeping of syringes in spirit, all of which have been repeatedly condemned, should be abandoned.

REFERENCES

Albury, M. (1947) *Lancet*, ii, 597.

Bourdillon, R. B. (1948) *Spec. Rep. Ser. med. Res. Coun., Lond.* 262, 316.

— Colebrook, L. (1946) *Lancet*, i, 561.

British Pædiatric Association (1946) *Brit. med. J.* i, 673.

Central Health Services Council (1950) Report on Infection in Hospitals. H.M. Stationery Office.

Court, D. (1949) *Lancet*, ii, 874.

Department of Health for Scotland (1947) Neonatal Deaths due to Infection. H.M. Stationery Office.

Evans, R. J., Spooner, E. T. C. (1950) *Brit. med. J.* ii, 185.

Garrod, L. P. (1944) *Ibid.* i, 245.

Green, J. B. M., Penfold, J. B. (1947) *Lancet*, ii, 89.

Higgins, M., Hobbs, B. C. (1950) *Mon. Bull. Min. Hlth*, 9, 38.

Lancet (1949) ii, 803.

Medical Research Council (1941) Prevention of Hospital Infection of Wounds. War memo. no. 6. H.M. Stationery Office.

— (1944) The Control of Cross-infection in Hospital. War memo. no. 11. H.M. Stationery Office.

— (1945) The Sterilisation, Use, and Care of Syringes. War memo. no. 15. H.M. Stationery Office.

— (1948) *Spec. Rep. Ser. med. Res. Coun., Lond.* 262.

Rountree, P. M. (1947) *Med. J. Aust.* i, 427.

Spence, J. C. (1947) *Brit. med. J.* i, 125.

van den Ende, M., Lush, D., Edward, D. G. ff. (1940) *Lancet*, ii, 133.

Watkins, A. G., Lewis-Faning, E. (1949) *Brit. med. J.* ii, 616.

SCOTTISH REGIONAL HOSPITAL BOARDS

The Secretary of State for Scotland has made the following appointments to the five Scottish boards. Out of 36 appointments, 18 are reappointments of retiring members. Those now appointed will hold office until March 31, 1955. The names of doctors are shown in bold type.

NORTHERN REGION

Reappointed: N. MacIver.

New members: **A. Lamont**, M.B., J.P.; Rev. W. MacLeod; **R. C. Murray**, F.R.C.S.E.; E. Macintosh (to March 31, 1953); two appointments outstanding.

NORTH-EASTERN REGION

Reappointed: James M. Burnett; Alexander Lyon, D.S.O.; Mrs. **Helen M. Taylor**, M.D.

New members: Prof. A. Cameron; **G. I. Davidson**, M.B.; J. L. Hill; R. Muir Wilson; Sir Hugh Turnbull, K.C.V.O., K.B.E. (to March 31, 1953).

EASTERN REGION

Reappointed: J. J. Duffy; James E. Prain; Provost W. J. Ross.

New members: Mrs. A. M. Allardice; **A. R. Moodie**, F.R.C.S.E.; **James Simpson**, M.B.; **A. F. Wood**, M.B.

SOUTH-EASTERN REGION

Reappointed: O. A. Cunningham; Prof. **D. M. Dunlop**, F.R.C.P.; J. McKelvie, J.P.; J. Sneddon.

New members: **J. J. R. Duthie**, F.R.C.P.E.; Major D. Russell; J. P. Watson; Councillor R. Burnside, J.P. (to March 31, 1953); two appointments outstanding.

WESTERN REGION

Reappointed: Prof. J. Aitchison, B.SC., L.D.S.; J. Dunlop; Ex-Provost Fyfe, M.B.E.; F. Gormill; W. McLaughlin; **A. Miller**, F.R.F.P.S.; Prof. **G. M. Wishart**, F.R.F.P.S.

New members: R. J. Hastings, M.B.E.; **Carrick McDonald**, M.B.; P. McKenna; Captain J. P. Younger, C.B.E., D.L.; **P. K. McCowan**, F.R.C.P. (to March 31, 1953).

THE LISTERIAN FESTIVAL

Since 1924 the Royal College of Surgeons of England has awarded, once in three years, a Lister medal in recognition of distinguished contributions to surgical science. As this year's recipient, Sir James Learmonth, delivered his Lister Oration at the college on April 4. We hope to publish it next week.

At the Festival dinner in the evening Mr. Harry Crookshank, the Minister of Health, proposed The College, towards which he expressed much kindness. Sir Cecil Wakeley, responding as president, said that when Lister joined the council in 1880 there were 1200 fellows, but now there were 3500. The Nuffield College of Surgical Sciences would accommodate 75 postgraduates, and the address of the college would be 35–45 Lincoln's Inn Fields. He hoped that the Lister Oration of 1955 would be given in its new great hall. Mr. Philip Mitchiner proposed The Guests, including two members of the Lister family, A. R. Lister, F.R.C.S., and W. A. Lister, F.R.C.P. Lord Simonds, the Lord Chancellor, was careful to disclaim responsibility for the Lords' decision on the previous day that the college is a charity. Mr. A. L. Geyer, High Commissioner for South Africa, spoke of the debt owed to the college by the profession in his country. Sir James Paterson Ross, vice-president, paid a moving tribute to the Lister Orator—a welcome representative of surgery, he said, in Europe and America, and known even in Scotland. How were all these wonderful things done? Partly perhaps by living 400 miles from London, which enabled Sir James Learmonth to read in transit *The History of the Peloponnesian War*. Responding, the Lister Orator said that he would carry back to Edinburgh the college's good wishes to the school of which he came as representative.

Before our Time

LEONARDO'S LEFT HAND

Norman Capener

F.R.C.S.

This week the 500th anniversary of the birth of Leonardo da Vinci on April 15, 1452, has been celebrated throughout the world. Leonardo was an artist of supreme genius and he was pre-eminent equally as a scientist. These aspects of his work are marvellously displayed in the exhibition now at Burlington House, and doctors, no matter what their special interest, will find there much to fascinate them, quite apart from the æsthetic interest of the exquisite drawings—the products of his "ineffable left hand."

It is commonly thought that Leonardo was left-handed, and the great authority A. E. Popham writes:

> "One factor in Leonardo's drawings is, however, constant, his left-handedness. He apparently never drew with his right hand and the strokes of the pen or other instrument where they can be distinguished, slope down from left to right, not in the normal direction from right to left."

But though it is, of course, true that Leonardo usually used his left hand, I am not at all sure that he was properly a left-handed person. By this I mean, from the neurological viewpoint, he was not clearly a right-cerebral-hemisphere-dominant individual. In the modern world, dominance of the right hand probably assumes a greater significance than it did in the ages when craftsmanship was all-important. We have become too conscious of our right hand, because of its association with the written and spoken word. As Focillon, the French writer on æsthetics, has neatly put it:

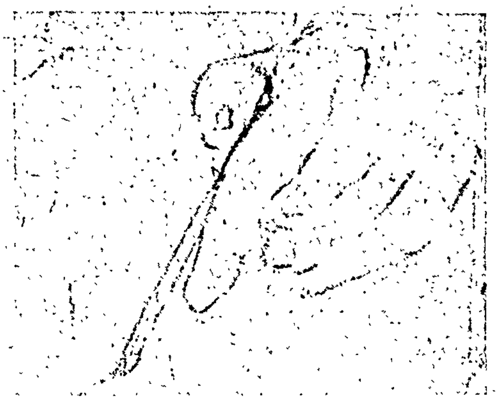
> "The hands are not a pair of passively identical twins. Nor are they to be distinguished like younger and older children or like two girls with unequal talent, one trained in all skills, the other a serf dulled by the monotony of hard work. I do not believe altogether in the eminent dignity of the right hand. *Deprived of the left it retires into a painful, almost sterile* solitude. The left hand, which signifies unjustly the evil side of life, the 'sinister' portion of space, the side from which one must not come upon a corpse, or enemy or bird—the left hand can be made to perform all the duties of the right. Fashioned like it, it has the same aptitudes, which it renounces in order to assist its partner."

In craftsmanship the two hands develop their own special skills which by habitual use cannot very readily be transposed. Such bimanual skill is different from ambidexterity in which either hand can do a job equally well, or more often, some people believe, equally imperfectly.

How does all this apply to Leonardo? Was he a right-cerebral-hemisphere-dominant individual? I believe there is reasonable doubt about this, and that to dismiss him as left-handed (as has so often been done) is to take too superficial a view of the matter—though after 500 years it may be impossible to answer the question with certainty.

THE EVIDENCE OF THE DRAWINGS

I have long studied Leonardo's drawings in reproduction. It has, however, been a great revelation to see so many of the originals. Some years ago when I first believed it possible that Leonardo was primarily a right-handed person, I noticed that Richter in his *Literary Works of Leonardo da Vinci* states that Leonardo's earliest notes at the age of 21 were written mirror fashion. Richter discounted secrecy because there is no reason to believe that Leonardo wanted to hide his investigations from other people; and in any case mirror-writing would have been a poor way of doing this. Richter thought that the right hand might have been crippled in an accident, and he quotes Leonardo's remark that he



(Science Museum Photograph

“ thanked God for having escaped from murderers with only one hand dislocated.” With this in mind I was particularly interested to examine the reproduction of a drawing of the *Left Hand*. (No. 360 in the Burlington House exhibition; no. 283v.b. in the *Codex Atlanticus* from the Biblioteca Ambrosiana, Milan.) The annotation in the catalogue is as follows:

> “ The drawing of a left hand holding a pencil is of interest as Leonardo’s left-handedness was presumably one of the reasons why he habitually wrote mirror-writing.”

My interpretation is somewhat different, though I agree that the drawing is of one of Leonardo’s hands; for the pencil suggests that. An artist doing a self-portrait, whether of his face or hand, would draw what he sees in a mirror, which, in Leonardo’s day would probably have been called a speculum. Most artists have mirrors in their studios, which they use not primarily for self portraiture, but for the study of their work from unusual viewpoints. I am convinced that the drawing is a self portrait of Leonardo’s right hand drawn with his left hand.

An interesting feature is that the hand illustrated is somewhat deformed by the middle finger being twisted and shortened. The presence of a pencil in the right hand does not surprise me. There are difficulties in using a pencil for the finer movements of shading and writing, which are largely phalangeal movements, without the support of the middle finger; and the middle finger of the drawing may well have got in the way. Nevertheless, as all teachers of art impress upon their students, to draw outlines with breadth and freedom, the use of the whole upper limb from the shoulder is encouraged. I believe that for the more dynamic drawing of shape and structure Leonardo probably used his right hand, but for the contemplative aspects of shading and writing he used the left hand.

If my interpretation supports the story quoted by Richter, is it not possible that the clinical history was somewhat as follows? An injury to the right hand involved a fracture with shortening, deformity, and stiffness of the interphalangeal or metacarpophalangeal joints. A temporary but serious incapacity of this sort would lead a man of Leonardo’s character and interests immediately to learn to use the left hand, which he would find most easy to do in mirror fashion for both shading and writing if he were primarily right-handed. If the disability in the right hand persisted to some extent he would probably continue to use the left hand for these tasks.

HIS HANDWRITING

Leonardo’s writing was done chiefly for his own record and information, and not for other people’s information. He did, however, on occasion use the orthographic style, notably when he wished his writing to be read by somebody else. The letter in which he offered his services to the Duke of Milan (no. 307 in the exhibition) is not written in mirror-writing, but I do not believe that we must therefore deduce that “ It is almost certainly not in Leonardo’s handwriting.”

Leonardo was not a modern pigmy limited to the use of one hand. He was a superb craftsman. He must have had a high degree of bimanual skill. I believe, with Richter, that an accident in early life may well have led him to begin to use his left hand for some purposes and was thus the means of developing to their utmost the cerebral functions of which he was capable. Whether this implies innate left-cerebral-hemisphere dominance is perhaps too speculative a question to pursue here. Nevertheless Leonardo was a complex character who cannot be dismissed simply as “ left-handed.”

BIBLIOGRAPHY

Focillon, H. (1948) Life of Forms in Art. New York.
Popham, A. E. (1952) Catalogue of Leonardo da Vinci Quincentenary Exhibition, Royal Academy of Arts.
Richter, J. P. (1939) Literary Works of Leonardo da Vinci. London.

Medical Conferences

THE SUPRARENAL CORTEX

COLSTON RESEARCH SOCIETY SYMPOSIUM

THE fifth annual symposium of the Colston Research Society of the University of Bristol was held at Bristol from March 31 to April 3. The subject was The Suprarenal Cortex, and the symposium was directed by Prof. J. M. Yoffey, professor of anatomy at Bristol. The members were welcomed by the vice-chancellor of the University, Sir PHILIP MORRIS.

PREPARATION AND PROPERTIES OF A.C.T.H.

Dr. C. H. LI (California) compared the ascorbic-acid depletion test with the other biological tests and concluded that it provided an inadequate estimate of A.C.T.H. activity. The lack of correlation in these assays suggested to him that there may be more than one A.C.T.H. He described Astwood’s oxycellulose procedure as a great advance in the preparation of a purified fraction. By this method the activity of the final fraction reached 64 units per mg. The final fraction was a polypeptide with a molecular weight of 10,000 and a pH of 9.

Prof. F. G. YOUNG, F.R.S. (Cambridge), said he was still satisfied with the ascorbic-acid depletion test (A.A. factor) and the adrenal weight test (A.W. factor) in hypophysectomised rats. He described the use of ion-exchange resins for fractionating A.C.T.H.-containing material. He and his colleagues had recently shown that two different fractions were retained and there was also a suggestion of different cellular effects—the “ adrenal-weight ” fraction stimulating mitotic activity, and the “ ascorbic-acid ” fraction having little influence on mitosis.

Mr. C. J. O. R. MORRIS, PH.D. (London), described the methods which he had used in the preparation of A.C.T.H. By electrodialysis it had been possible to increase the activity of the fractions from 1·5 to 25 units per mg. The active fraction appeared to be strongly basic with a molecular weight of under 10,000, but it was too early to say whether it was protein or polypeptide.

The chairman of this session, Dr. E. B. ASTWOOD (Boston, Mass.), said that the therapeutic effect of extracts of widely varying potency correlated remarkably well with the ascorbic-acid depletion test. It was possible that the other factor was provided by the patient’s own hypophysis. He described the production of purified corticotropin, growth hormone, intermedin, and a fat factor, adipokinin, by his oxycellulose method.

THE STRUCTURE OF THE CORTEX

Professor YOFFEY described as surprising the persistence of the old notion that the cells of the adrenal ortex migrate from without inwards. He pointed out hat histologically there was a sharp demarcation between he three layers of the cortex. The evidence provided by .C.T.H. stimulation suggested that the zona reticularis was the main site of activity, and radioactive studies howed that labelled A.C.T.H. was localised in the zona eticularis. He wondered why the most active part of he cortex lay in contact with the medulla. He concluded rom histochemical studies that the most active area was transitional zone between the zona reticularis and the ona fasciculata.

THE NATURE OF THE HORMONES

Prof. F. VERZAR (Basle), in describing the hormones ctually secreted by the adrenal cortex, said that Dr. I. E. Bush, working at the M.R.C. Institute, had identified orticosterone and 17-oxycorticosterone in the blood y chromatographic analysis; there was no need to ssume the presence of a deoxycortone-like hormone in the ody since both these substances could control electrolyte evels adequately. As far as the influence of the androgen unction of the cortex was concerned, adrenalectomised nimals, kept alive for years by deoxycortone acetate, ad normal sex and reproductive functions. The corticosteroids acted directly on glucose or glycogen production nd inhibited glycogen metabolism under all conditions. Their other major metabolic effect was on electrolytes, nd this action was closely related to their influence on arbohydrate metabolism. Potassium enters the cell with lycogen and leaves it when glycogen is mobilised. The site of corticosteroid action is in the cell, and the ffects are brought about by enzymes.

Dr. HUDSON HOAGLAND (Worcester Foundation) eported that work with perfused human adrenals at he foundation had shown that A.C.T.H. removes the ide-chain from pregnenolone to make progesterone. Progesterone is the key substance, and 17-hydroxycorticosterone and corticosterone are formed from it.

Dr. D. H. NELSON (Utah) described how he had, by chromatographic methods, examined the blood from the adrenal vein of animals, including the cow, and isolated three groups of hormones.

CONTROL OF SECRETORY ACTIVITY

Dr. MARTHE VOGT, F.R.S. (Edinburgh), reviewed our knowledge of the control of the adrenal cortex. Adrenaline increases the flow of A.C.T.H., and in the absence of adrenaline the adrenocortical response is diminished but does not completely disappear. Another regulating mechanism works through the hypothalamus, and there is a third depending on the level of A.C.T.H. in the blood—a metabolic regulation—but it is not known whether the site of this action is the anterior pituitary or the hypothalamus. Experiments with the isolated and perfused adrenal indicate that the cortex goes on synthesising hormones at the usual rate but is then not affected by environmental changes.

Dr. D. J. INGLE (Michigan) thought that the anterior pituitary transplant experiments were not entirely satisfactory since it was difficult to extirpate completely any endocrine organ. He thought the anterior pituitary was receiving something from the hypothalamus which was enabling it to function.

RÔLE IN INFECTION

Dr. H. J. ROBINSON (Merck Institute) discussed the rôle of the adrenal glands in infection, and described experiments on rabbits whose skin was inoculated by type-I pneumococcus. In animals receiving 5 mg. of cortisone daily the response was more severe than in untreated animals, and by the fifth day all the treated animals were dead, while the controls had no more than a transient bacteræmia. Studies of the response of the host to an infection showed a similar inhibition of the defence mechanisms, including delayed appearance of neutrophils and lower antibody titres. Dr. Robinson thought that more recent experiments indicated that though large doses of cortisone inhibited the inflammatory reaction, it might be possible by small and repeated doses to stimulate the adrenal cortex, with enhancement of the defence mechanisms.

In discussion Dr. J. J. R. DUTHIE (Edinburgh) said that it was now well understood that the inflammatory reaction to bacterial invasion could be suppressed by cortisone, but it should also be realised that it may have evil long-range effects in inflammations whose cause is unknown and where damage may continue despite pharmacological suppression of the inflammatory reaction.

Prof. G. R. CAMERON, F.R.S. (London), chairman of the session, also emphasised the need for caution in the interpretation of the effects of cortisone upon inflammatory processes.

PSYCHIATRIC DISORDERS

Dr. HOAGLAND discussed the relation of the adrenal cortex to disorders of personality. He thought the electro-encephalographic changes in the adrenalectomised animal and in Addison's disease were produced by anoxia due to slowing of cerebral circulation. The cerebral blood-flow was restored by adrenocortical extract, by cortisone, and by pregnenolone. In 200 schizophrenic men there was evidence of altered steroid metabolism when compared with 200 controls. Dr. Hoagland described a test used to produce psychological frustration. The patient was invited to play a game on a pin-table, and while the investigator made success easy at the start, conditions were made increasingly difficult by an unseen tilting of the board. He agreed that the metabolic disturbance might be primary or secondary, but this matter was now being tested. In Chicago last year 6 schizophrenics on whom total adrenalectomy was performed were being maintained in good physical health by deoxycortone acetate and cortisone. No comment on their present mental state was made.

Dr. R. E. HEMPHILL (Bristol) described the changes in adrenal cortical function in shock and hormone treatment, and concluded that although there were varying degrees of response to adrenocortical stimulation in mental disorders, a poor response indicated a poor prognosis. He inferred that electroconvulsive therapy (E.C.T.) affected the responsiveness of the adrenal cortex, but said that A.C.T.H. was not to be regarded as a therapeutic substitute for E.C.T.

Dr. MAX REISS (Bristol) emphasised that there were important constitutional and environmental factors which, together with a variable sensitivity of the tissues to hormonal activity, provided a pattern which was more important than any element in it. He thought that in mental disorders this abnormal hormonal equilibrium might sometimes be reversed without treatment, with coincident remission of disease, but in other cases treatment with testosterone or œstrogen might be valuable in restoring normal equilibrium.

Dr. A. SEGALOFF (New Orleans) said he was very disturbed by the conclusions which had been drawn about the relation of the adrenal cortex to mental disorder. He compared the altered steroid excretion reported in such disorders as carcinoma, and asked, in the manner of a Huxley, "where are your controls?"

THE ADRENAL CORTEX AND THE GONADS

Prof. S. ZUCKERMAN, F.R.S. (Birmingham), protested against the activities of the chemists who were busily disintegrating and fractionating until all physiological reality had disappeared from their products. Biological criteria must in the end be the standard of activity, and he asked for less disarticulation and more synthesis. He described the stimulus of A.C.T.H. and the gonadotropins

to the adrenal cortex and the gonads, and suggested that each of these hormon
sone-like and gonad
There was no rigid ph
pituitary hormones and, under stress, any switch of activity was possible. He refused to define stress; by some definitions "stress might be caused by taking three meals a day."

Professor **Young** replied for the chemists, saying that experiments of disintegration were essential; when the purified fractions were identified, the biological activity of each fraction could be tested and the process of reintegration could begin.

Dr. F. T. G. **Prunty** (London) insisted that the ultimate criteria must be biological. Much reliance was placed on the ascorbic-acid depletion test, but what in fact was the relationship between ascorbic acid and the adrenocortical steroids? The adrenal cortex of the scorbutic guineapig continued to function very nicely. He had shown, as Professor Zuckerman had said, that the ovary in the adrenalectomised animal could at least partially undertake the functions of the adrenal cortex.

Mr. S. J. **Folley**, D.SC., F.R.S. (Reading), described experiments on mammary gland slices, and concluded that cortisone depresses the synthesis of fatty acids from small molecules. Complete lactation had, however, been maintained in the adrenalectomised rat by the administration of cortisone and deoxycortone. Enzymic activity in the gland, as estimated by arginase formation, was stimulated by cortisone.

Dr. A. **Puck** (Bonn) reported that the excretion of 17-ketosteroids in women with uterine carcinoma was reduced below average levels.

ESTIMATION OF URINARY CORTICOSTEROIDS

Prof. G. F. **Marrian**, F.R.S. (Edinburgh), described a method for estimating the 20-methyl steroids in urine. He criticised the acceptance of the level of formaldehydogenic steroids in urine as an estimate of adrenocortical activity, because the amount is small compared with those used in methods of biological assay, and because there is an appreciable loss when the urine is allowed to stand. He opposed the use of the method of glucuronidase hydrolysis for routine estimation of corticosteroids, because it was not yet standardised.

TISSUE CHANGES

Professor **Cameron** discussed the tissue changes in animals and man during A.C.T.H. and cortisone therapy. He concluded that cortisone inhibits the response to injury and in large doses it retards the early stages of repair. These effects are produced in the cell and probably on cell membranes; further elucidation of the action of cortisone would come from the cytologist.

Dr. P. L. **Krohn** (Birmingham) had studied the effects of the steroid hormones on skin grafts in the rabbit. He had found that cortisone increases the survival-time of homografts fourfold by an alteration in the "afferent side of the immunity reflex arc"—not in the host immunity responses.

Dr. O. A. **Trowell** (Harwell) showed that the effect of large amounts of cortisone on lymph-nodes growing in a culture medium was to cause pyknotic degeneration in 30% of the cells after 48 hours.

Professor **Yoffey** and his colleagues had found that A.C.T.H. injected for 7 days increased the numbers of erythroid cells and lymphocytes in the bone-marrow. Professor **Cameron** suggested that the increase in the lymphocyte-count might indicate a compensatory response to increased destruction.

HOMŒOSTASIS

Dr. D. J. **Ingle** (Michigan) described some of the effects of the adrenal cortex in homœostasis. In discussing Selye's concept of the "adaptation" diseases, he suggested that the increased secretion of adrenocortical hormones in these diseases did not represent a true hypercorticalism. Increased secretion was rarely a primary agent in disease, and its function was usually to support the resistance of the body against a noxious process.

Prof. H. S. **Heller** (Bristol) described the depression of glomerular and tubular function in Addison's disease and in adrenalectomised animals. He concluded, from experimental evidence, that the changes in the extracellular fluid may have a determining effect on the reabsorption of sodium and water in the tubules. His experiments with vasopressin might indicate that the tubular cells are more sensitive to vasopressin in adrenocortical deficiency. The evidence for compensatory overactivity of the neurohypophysis in adrenalectomised animals must be regarded as uncertain.

Dr. G. A. **Smart** (Newcastle) reported that while the average total potassium content of the body was 45 m.eq. per kg. body-weight, in two patients with Addison's disease the figure was 57 m.eq. and 56 m.eq., and in two patients with Cushing's syndrome, 29 m.eq. and 31 m.eq.

Dr. A. A. G. **Lewis** (London) suggested that there was a diminished flexibility of tubular reabsorption in Addison's disease. There was a facultative power of reabsorption of sodium and water in the distal tubules. In health, each is separately reabsorbed; in Addison's disease both are absorbed together. Deoxycortone only restores the power to absorb sodium, while cortisone completely restores the flexibility of the system.

TREATMENT

Mr. L. R. **Broster** (London) described the surgical treatment of female pseudohermaphroditism, of the adrenogenital syndrome, and of Cushing's disease. The incidence of psychotic disorders in hypercortical syndromes was a little less than 25%. The results of surgery in carcinoma of the adrenal cortex were very unsatisfactory, but the risks of bilateral subtotal adrenalectomy were small. It may be that the treatment of adrenocortical hyperplasia by cortisone has made the indications for surgery narrower, but surgery of the adrenal cortex has stimulated scientific research in several directions.

Dr. **Astwood** discussed some of the newer results of treatment by A.C.T.H. and steroid hormones. Corticosterone and hydrocortisone (compounds B and F) had been shown to have the normal major secretory effects of the adrenal cortex, and were effective by mouth. In the treatment of Addison's disease, 50 mg. of cortisone daily made other treatment unnecessary, but with 25 mg. of cortisone daily, salt and D.O.C.A. might be required. In hypopituitarism, cortisone, the sex hormones, and thyroid gave a good result, but patients were not restored to full health; perhaps the growth hormone might supply what they lacked. Since intravenous therapy with cortisone was not available, it was necessary to give 300 mg. of cortisone daily for a few days before total adrenalectomy was performed. Hydrocortisone was more effective than cortisone when injected into arthritic joints. The treatment of asthma with aerosol inhalations had reduced the amount of cortisone required. The purification of A.C.T.H. had now made possible depot injections in oil or gelatin and much smaller doses were now required; the potency of the former impure products had been reduced by partial inactivation in the tissues at the injection site. He thought that for some years treatment by A.C.T.H. would be cheaper than by cortisone.

Dr. G. D. **Kersley** (Bristol) discussed some aspects of the clinical response in rheumatic diseases. He described two cases in which complete resistance to A.C.T.H. and cortisone had occurred.

In England Now

A Running Commentary by Peripatetic Correspondents

THE fiesta in Pamplona starts at noon. At 11.59 the narrow streets of the old town are packed with people quietly waiting for the signal. Then the noon-gun is fired, out come the red neckerchiefs, and in an instant veryone is dancing wildly. It is hard to believe unless you have seen it, but the dancing goes on almost coninuously for five days and nights. Whether you look out of your window at 5 in the morning or 11 at night you will see the same figures wildly leaping up and down. Now and then somebody falls asleep on the pavement, but he soon wakes up and starts dancing again with renewed energy. There are two periods in each twenty-four hours when the dancing stops for the evening bull-fight; and for the *encierro,* the amazing ritual in which he local lads allow themselves to be chased through the old town into the bull-ring by the six bulls that are to be fought in the evening's formal corrida. Afterwards, over breakfast in the cafés, the Spaniards tell one another how the black bull gored three men, and how two more came to be dying in the infirmary. Everyone agrees that it was a wonderful encierro.

Horn-wounds incurred in the bull-ring are usually extensive lacerations between knee and groin, with now and then a penetrating wound of the chest or abdomen. Not having been in Spain for some years I wanted to know the modern surgical treatment for these injuries. Multiple wounds like those from which the great bull-fighters, Joselito and Manolete, died in the ring are bound to be fatal. But in the old days many matadors died slowly from sepsis. Modern treatment could surely have saved Gitanillo, for example, who died in September after being wounded in May. Then there was Luis Freg, who returned to the ring as daring as ever after each of his 72 wounds, though in the end contractures left his legs gnarled and twisted like the branches of an old oak-tree, and his chest and abdomen covered with the scars of the wounds that should have killed him. Surely penicillin would have spared him much of his suffering and disablement? I called on the surgeon in charge at the bull-ring to find out what happened nowadays. He showed me his new operating block at the back of the ring and I told him truthfully that I should be proud to have so perfectly equipped a theatre in my own hospital. He said that the debridement techniques learnt in the Civil War, supported by the antibiotics, have vastly reduced both the mortality and the duration of incapacity from bull-fight wounds. The better chance of quick recovery seems also to have affected the matador's own technique. His cape-work is done far closer to the bull—so close, in fact, that in some passes with the muleta the bull appears to be wrapped round the matador. This side of the fight has gained importance at the expense of the actual killing, which is often bungled. By making the bull-fighter's job safer, penicillin has led the spectators to forget how the whole business should end—with a single sword-thrust that lays the bull dead at the matador's feet.

* * *

An anatomist friend of ours underwent a testing experience the other day. He was sitting in his room doing whatever anatomists do when they disappear from the dissecting-room, when a scrabbling noise made him turn round to observe, sitting on the bench beside his microscope, a large monkey. In the psychiatric and occult literature such an occurrence is, of course, scarcely worthy of comment, but the general run of exteriorised monkeys tend to be small and malignant, with portions of the background furniture showing through. This animal was a ponderous and apparently well-disposed macacque; moreover, it appeared to be pregnant—a circumstance hitherto unrecorded of exteriorisations. Anatomists lead a sheltered life, but they are not devoid of resource: hastily connecting his open door with the repairs to the animal-house along the passage, our friend reached gently for the telephone and informed the animal-man of the whereabouts of his charge.

The cautious arrival of heavily breathing reinforcements, armed to the teeth with nets and poles and sacking, was accomplished outside the door without incident until an injudicious spectator dropped something and swore. At once the placid mother-to-be was converted into a grey blur travelling at great speed round the walls and dislodging copious showers of reprints, boxes of slides, and an anencephalic fœtus. The blur eventually shot past our friend's head on to the floor and ran unexpectedly between the feet of the posse to a refuge on top of the large steriliser in the passage. Here it instantly regained its maternal placidity and benign appearance.

By this time there was a large gallery, and much advice was freely given and freely rejected. The embryologist devised an ingenious trap of sacks and netting to be released by a piece of string on the approach of the monkey—a consummation which did not eventuate. A visiting physiologist, armed with a large silk handkerchief, climbed confidently on top of the steriliser, but was swiftly outmanœuvred and fell, spraining his ankle. The anthropologist, who had been to America, demonstrated the technique of the *bolo* with a string bag to which he had tied two small cabbages, and the neurohistologist, inspired by a visit to *Quo Vadis*, used a net and pole and landed some challenging lunges on the spectators. The proceedings were terminated when the animal, mildly irritated, took a leap for a totally inadequate electric light and fell squarely into an open food-bin which our friend (a mere topographist) had the presence of mind to close.

* * *

You remember the Thurber household who had cats the way most people have mice? For some time now we have had electrophysiologists on a similar basis, and our conversation has become adjusted to include such things as "negative feed-back," "noise level," "stimulus artefact," and "monophasic degeneration." Now, however, an electronic expert has arrived to service the electrophysiologists, and our hardly acquired small talk recoils abashed before the real stuff. He keeps his electrons—and his electrophysiologists—in a series of dank and noisome chicken-runs in the basement, surrounded by notices bearing an intimidating number of volts. At his bidding Wellsian structures amplify the neural mysteries. But our awe of him really dates from the day he altered the earthing of the chicken-wire. Instead of the customary physiological shrieks and growls a burst of dance music filled the building—he had got Radio Luxembourg.

* * *

This is the season for spring onions to make their coy appearance on greengrocers' stalls. Those of us whom the disapproval of family, colleagues, and patients cannot restrain from shameless indulgence should reflect on the fate of four Chicago doctors. These stalwarts each ingested 2 lb. of cooked onions daily for a week and found that their red-cell counts fell about a million per c.mm., causing a noticeable pallor. Happily, all four had completely recovered ten days after laying off the extra veg.

In fairness to these worthy men it should be added that their unprecedented intake of onions was wholly motivated by the quest for an anti-hæmopoietic factor to cure polycythæmia; gluttony was not even a secondary factor. Strong evidence of their selfless devotion to science is the fact that they ate their onions cooked, though it is just possible that spring onions are not grown in Illinois.

* * *

Poultry farmers have known for years that egg production can be increased by "lighting-up" their pens with electric lights switched on before sunrise. This simple trick fools the hen into thinking that dawn has come, and she lays the morning egg forthwith. Human beings are notorious for producing their infants at dead of night; so we are considering blacking out our maternity unit by day and keeping bright lights blazing in it all night. Shall we fool the mothers? I wonder. And, supposing we do, shall we raise the local birth-rate?

* * *

I was puzzled when I arrived home to find my wife doing needlework with the aid of my long-neglected *Gray's Anatomy*. Our son has now reached the age when he wants a Jolly Roger to fly over his tent.

Letters to the Editor

VARICOSE ULCERS

SIR,—You state in your annotation of April 5 that a few weeks in bed will heal most varicose ulcers, but that the rest must be absolute and the leg raised. It is, of course, the impossibility of this in early middle life which leads to the chronic ulcer of late middle life, and I should have thought that the secondary dangers of absolute rest—e.g., fixation of arthritic joints in the neighbourhood of the septic ulcer—might well outweigh its advantages.

So far as general practice is concerned I should like to emphasise that most ulcers can now be healed with ambulant treatment if judicious use is made of the different types of supporting bandage and of systemic penicillin and anti-histamine compounds where indicated. This takes longer than rest in bed—perhaps three to nine months—but with patience the ulcer is healed, and the patient is then immediately supplied with an elastic stocking and referred to the surgeons, who in Newcastle are particularly coöperative in wasting no time in dealing with such cases. For the practitioner the essentials to bear in mind are the principles of support, controlling infection and secondary allergic manifestations, and personal attention; it is important that he should himself apply the bandage, since even minor defects in its application can cause unnecessary discomfort; if one bandage proves unsuitable he must patiently try another. His personal influence is important at such times in encouraging a patient not to discard treatment altogether.

Thus with modern appliances and drugs, with a good supporting hospital service, and with the easy supply of elastic stockings under the National Health Service, the treatment of varicose ulcers or their prevention is an excellent example of a field in which the usefulness of the general practitioner has greatly increased in the last decade. This does not affect the cogency of your remarks about prevention, but commonly operation seems the only effective method.

Amble, by Morpeth,
Northumberland.
R. P. ROBERTSON.

SIR,—Your annotation does not do justice to present-day views. Nearly all authorities have emphasised the absence of varicose veins in most cases of varicose ulcers. When true superficial varicose veins are obvious, the skin in the lower third of the leg is usually remarkably healthy. Superficial varicose veins are a comparatively rare cause of varicose ulceration; the vast majority of varicose ulcers are due to incompetent valves in the deep veins.

These deep veins are rendered valveless, or their valves rendered incompetent, in several ways. Children start life with many more valves than are required to aid venous return against gravity; but with age there is a progressive diminution in the number of valves. If a child starts life with a small complement of valves, this progressive disappearance of them will lead to venous congestion. Venosclerosis, or vein hardening (which is as common as arteriosclerosis), allows stretching of the vein wall, rendering the valves incompetent. These two processes of valve atrophy and vein sclerosis are as relentlessly progressive as greying of the hair and age itself; nothing will delay them. These factors alone probably account for nearly 50% of varicose ulcers. Thrombophlebitis in the deep veins initially blocks the veins; and reflex arterial and venous spasm may cause a white-leg. In time these blocked channels are re-canalised from the groin to the ankle; this may take up to twenty years. The re-canalised channels will be completely valveless. The sad fate of 90% of patients with white-legs is a varicose ulcer years later. Injection with sclerosants of varicose veins may by diffusion through communicating channels destroy the delicate valves in the deep veins. A large proportion of varicose ulcers could be prevented by timely treatment of thrombo-embolic disease, and a clear understanding of the risks associated with sclerosant therapy.

It is helpful to remember that approximately 90% of venous blood returns to the heart from the leg by the deep venous channels; only 10% returns by the superficial saphenous system of veins. If the valves are destroyed or rendered incompetent in the deep channels, then in the standing position severe venous congestion results in the capillaries of the lower leg. This leads to capillary damage, œdema, and eventually ulceration. Incompetent valves in the superficial veins lead to obvious varicose veins and may be ugly. It is unusual, however, for the venous congestion to cause capillary damage and ulceration. When occasionally this does happen obliteration of these varicose veins will cure the ulcer. The majority of ulcers are due to incompetence of deep valves and then treatment is usually much more difficult. Attempts are made to destroy incompetent deep veins, and thus remove the large static columns of venous blood from the capillaries of the lower leg, by such procedures as section of the superficial femoral and popliteal veins. These operations are not consistently successful in curing "varicose ulcers."

Despite all the modern surgical advances, probably the best treatment for varicose ulcers is still initial rest in bed followed by the wearing of an elastic bandage when the patient is ambulant.

Shoreham-by-Sea.
A. J. PARTRIDGE.

THE DENTISTS BILL

SIR,—The leading article in your issue of March 29 contains many ingenious arguments but a few misstatements of fact and a number of statements and conclusions which appear to be lacking in justification.

In the first place you state that the number of practising dentists is about 10,000. This is certainly a considerable understatement. There are in fact over 15,000 dentists on the Register, and it is by general consent agreed that the number of these in active practice is probably between 12,000 and 12,500, as was the position when the Teviot Committee presented its report in 1946. Moreover, I note that you state in one sentence that the Dental Schools "have no vacant places," and three sentences later that "the dental schools already have difficulty in filling all their vacant places with students able to follow the course of training." Official sources state that there are at the present time 2·4 applicants for every vacant place in the dental schools. In some schools the percentage is very much higher, ten or more applications being received for every place that is available.

Again, you state that it is "unrealistic to expect that the demand of adults for treatment under the National Health Service will be greatly reduced by the proposed charges." On the contrary, I think there is every evidence that the demand will be considerably reduced. The imposition of charges for dentures has already had the effect of reducing the gross earnings of dentists in the health service by something like one-third, and on this experience alone it may very reasonably be anticipated that a still further serious reduction in demand will result when the new charges come into operation. At the present time many dentists working in the general dental service are much less than fully occupied and would welcome the opportunity of giving to school-children the comprehensive treatment they alone are legally entitled to give.

Finally, to suggest that because many women dentists continue in practice after marriage "it is not unreasonable to expect an equally high proportion of dental nurses to continue their work in the same way" is at variance with all experience. Many women doctors continue in practice after marriage, but the proportion of nurses who do likewise is very much smaller.

I observe that you make no mention at all of the economic aspects of the proposal contained in the Bill. It amounts, in brief, to a suggestion that on the one hand one can, at a cost of £x, give two years' training to ancillary workers who will then be able to carry out two dental operations on children or one dental operation on adults and who may give service for ten years or something more. On the other hand for an expenditure of £2x a dental surgeon can be trained for five years and will then be able to give comprehensive service for a normal practising life of forty years.

Bearing in mind the inevitable lapse of time before any considerable numbers of these dental ancillaries are available for the school dental service, it is, I suggest, uneconomic and unrealistic to force the creation of such a class, whose usefulness has not yet been demonstrated in the conditions of this country, to meet a crisis which may very well be a matter of long-past history before they are available.

British Dental Association,
13, Hill Street,
London, W.1.

H. T. Roper-Hall
President.

THE CHARGES

Sir,—As reported under the above heading in your issue of April 5, Dr. Edith Summerskill and Mr. Bevan seem to supply an answer which should appeal to all sections of the community.

Mr. Bevan suggests that it would be logical to put drugs out of the National Health Service scheme. Dr. Summerskill states that in residential areas the cost of prescriptions is more than three times what it is in industrial areas; which means that if drugs were outside the scheme the loss to the better-off would be three times as great as the loss to the industrial community.

Doctors would like to prescribe less and have more time for the examination of their patients. To omit drugs from the scheme would represent a great saving in cost to the N.H.S.; and to offset hardships it should not be difficult to devise a method of subsidy against the high cost of those drugs deemed from time to time to be of the greatest value in treatment. The prescribing of many proprietary remedies of doubtful usefulness would be discouraged.

Reading.   Stanley Alcock.

EARLY DUMPING SYNDROME AFTER GASTRECTOMY

Sir,—We have read with great interest the article by Mr. Goligher and Dr. Riley (March 29). If their conclusions are correct, the term "dumping syndrome" is an exact description of the mechanics of the condition, and we are back where we started—in the illustrious company of Sir Arthur Hurst.

Unfortunately their whole investigation appears to have been based on the false premise that the behaviour of a barium "meal" is comparable to that of ingested food. The sensation of fullness after meals experienced by nearly all gastrectomised patients usually disappears in time; and we have always assumed that the sensation, and its subsequent disappearance, were due to the small size of the stomach, and its gradual anatomical and physiological adaptation to the increased load which it is called upon to bear.

It never occurred to us to doubt that barium cream would be retained in the stomach for a shorter period than a hearty lunch; but in an effort to produce some radiological support for this assumption, we have investigated a patient on whom one of us performed a subtotal antecolic Polya-Hofmeister gastrectomy two and a half years ago.

This patient, a member of the hospital staff, agreed to adulterate his lunch, consisting of sausages, mashed potatoes, and cabbage, with 2 oz. of barium sulphate. At the end of 20 minutes none of this meal had left the stomach. At 65 minutes a very little had passed through into the jejunum; and at the end of 2 hours about half the meal was distributed throughout the small intestine, whilst the remainder was still in the stomach.

We are well aware that one barium swallow does not make a statistical summer, but we have often observed distinct sphincteric action at the stoma after both Billroth I and Polya-type gastrectomies, and are of the opinion that any barium studies purporting to indicate the rate of emptying of the gastric remnant should be carried out after the ingestion of barium-impregnated food.

Barnet General Hospital.   V. J. Downie
Cedric Hilliard.

SPLENECTOMY

Sir,—In his paper (March 29), Mr. Maingot lists as no. 9 in the group of conditions where splenectomy is indicated "Primary tumours—e.g., lymphosarcoma." He does not discuss this further, and one is left with the impression that lymphosarcoma is a primary neoplasm of the spleen. Most workers regard this condition as a generalised disease closely related to lymphatic leukæmia. Indeed Willis[1] suggests that lymphosarcoma and lymphatic leukæmia should not be differentiated as the presence or absence of a preponderance of lymphocytes in the peripheral blood is quite fortuitous. This close relationship would be demonstrated more often if routine bone-marrow examination was done in all cases diagnosed as lymphosarcoma.

Perhaps Mr. Maingot considers that splenectomy is indicated if the disease apparently involves only the spleen when first diagnosed. If this is so, the results of this method of treatment would be most interesting.

Rarely lymphosarcoma is associated with a hæmolytic anæmia, and in such cases splenectomy may be of benefit. It is difficult, however, to see how splenectomy will influence the course of the disease in the majority of cases.

Cardiff.   O. D. Beresford.

OPPORTUNITIES IN GENERAL PRACTICE

Sir,—Your issue of April 5 includes an account of the debate in the House of Lords on the administration of the National Health Service. During this debate Lord Moran made some remarks about which I feel deeply.

It seems to me unforgiveable that people in high places should state that there has been an "insidious decline in the status of the general practitioner." There are, I believe, large numbers of extremely competent men in general practice, whose skill and knowledge entitles them to rank, in their own field, equally with the specialists. Regrettably, some are less able; and it may be this that has given rise to the impression of a decline in the status of the general practitioner. But then there are bad as well as good consultants.

General practice is an intensely interesting and rewarding branch of medicine in its own right, and, although much serious illness has to be referred to the hospital, an increasing number of conditions can be adequately nursed and treated at home. To the farsighted it will be apparent that if the present trend of medical progress continues the hospitals will be used less and less.

It may appear to the consultant that the general practitioner should be somehow given access to hospitals. But I, as a general practitioner, do not think this to be essential or even desirable. There is plenty of scope in the general practice of medicine, which ranges through the whole field from obstetrics and the care of the newborn to the care of the aged. All that is required is a wide interest.

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[1] Willis, R. A. Pathology of Tumours. 1948.

It is also in my view quite wrong to assume that the general practitioner cannot keep up to date unless he is attached to a hospital. There is no reason to suppose that only the specialist can be modern.

One further qualification of paramount importance in general practice is an abiding love of people, without which all is as naught.

Castle Bromwich. MAXWELL KENT.

BOVINE TUBERCULOSIS PREVENTS HUMAN TUBERCULOSIS ?

SIR,—Mr. Pitcher, in his letter last week, insists that the increase in admissions to hospital (Overdale) is evidence of an increase of tuberculosis in Jersey, in spite of the falling mortality-rate. Prior to 1925 there were no admissions to Overdale of tuberculosis patients; so if Mr. Pitcher's argument is valid there was no tuberculosis in Jersey in the year 1924, although according to the records there were 65 deaths from all forms of tuberculosis in that year.

In 1925, 8 beds were provided for tuberculosis at Overdale; from 1934 the number of beds provided began to increase, and we now have 49 beds solely for such cases. The figures given by Mr. Pitcher show our increasing care of the tuberculous and not an increase in tuberculosis. Before 1925 the great majority of patients were treated on a domiciliary basis only. Surely Mr. Pitcher does not expect anybody to accept the odd idea of a rapidly increasing incidence with rapidly decreasing mortality.

Sporadic cases of bovine tuberculosis in cattle have always occurred, and still do occur, in the Jersey herd. They are very rare, and there is no evidence that their number has either increased or decreased during the period discussed in Mr. Pitcher's letter.

R. N. MCKINSTRY

South Hill, Jersey,
Channel Islands.

Medical Officer of Health,
States of Jersey.

A VISIT TO PONT ST. ESPRIT

SIR,—The cause of a sudden outbreak of madness in August, 1951, at Pont St. Esprit in the Rhône Valley was traced to a certain consignment of bread. About 200 people were taken ill, of whom 4 died and 15 became temporarily insane. Victims were reported to have run through the streets crying that they were "on fire," and it was generally concluded that this was an epidemic of St. Anthony's Fire—i.e., ergotism caused by the infection of rye bread with ergot. It was alleged that "spurred rye" had been mixed with the flour used in the bread. But, as your annotation of Sept. 8 pointed out, the symptoms of this collective mania were not the classical ones of ergot poisoning, nor was ergot found on analysis of the bread.

In January I visited Pont St. Esprit and talked with Dr. Jean Vieu, many of whose patients were poisoned. He told me that they did *not* complain of feeling "on fire"; reports of this symptom seem to be without foundation. He gave me details of the psychological and mental disturbances which developed a week after the acute irritant poisoning, and which affected some 30% of patients. He described an initial "euphoria which then transformed itself into a nervous depression with anxiety and delusions of persecution."

One man was seized with claustrophobia and broke his leg when he jumped from an upstairs window. I later read of an old woman who kept seeing an immense silver-shod black horse as big as a mountain, and of a girl of 14 who told her mother she was flying over enormous singing flowers which clutched at her dress as she passed.

I do not think these people were poisoned by ergot. The symptoms are totally unlike those of any scientifically recorded cases of epidemics of ergot poisoning. I consider that the cause was Indian hemp (marihuana). This is the only known drug which could have produced these symptoms, with the possible exception of amphetamine, which can be excluded in the circumstances. Allentuck and Bowman[1] studied the effects of marihuana given by mouth, and concluded that "the main features of the poisoning are the restlessness and mental excitement of a delirious nature with intermittent periods of euphoria and an overhanging state of anxiety and dread." Their description is strikingly similar to that of Dr. Vieu. They also mention frequent visual hallucinations and occasional claustrophobia. The account given by Théophile Gautier in *Le Club des Hachichins* contains vivid and fantastic pictures very like those seen by some of the people of Pont St. Esprit.

Deaths from Indian hemp are rare but they have been reported. The severity of the outbreak suggests large doses; and the drug was taken in an unusual way —after being baked in bread for some hours. It is by no means unlikely that a strongly irritant compound was formed which caused the acute symptoms of general intoxication. The vomiting and diarrhœa probably eliminated the poison in most cases. In the less fortunate the delay in the appearance of mental symptoms may be explained by the impaired absorption of the remainder of the drug from the damaged intestine.

By what ghastly mistake hemp may have been mixed with the bread, one can only guess. But hemp can grow as a weed in the climate of central France; and recently a citizen was found growing the plant in innocence of its true nature. It is possible that the "spurred rye" was mixed with flowering hemp growing on the same ground.

Sutton, Surrey. DONALD McI. JOHNSON.

ANÆSTHESIA FOR TUBERCULOUS PATIENTS

SIR,—Dr. Mushin's letter of March 22 cannot be answered simply. Some months ago, thinking on the same lines, the anæsthetists of this area commenced a long-term study of the effects of inhalational anæsthesia for tuberculous patients; I am, however, quite sure that there are too many variable factors for any definite conclusions to be possible.

What factors, associated with inhalational anæsthesia, are liable to have a detrimental effect on a lung with active or quiescent tuberculosis?

1. There is the general metabolic disturbance; but an important factor here is the pathology which has made the operation necessary. Pregnancy and gastric ulcer are two examples; ill effects resulting directly or indirectly from these conditions must not be attributed to anæsthetic techniques.

2. During anæsthesia there may be morbidity from: (*a*) the drugs used (e.g., ether); (*b*) spread of sputum following coughing or vomiting, or failure to aspirate sputum; and (*c*) breakdown of cavities from straining, coughing, &c., during a difficult induction.

3. Postoperative vomiting and coughing might again cause spread of disease.

These factors are, I believe, the salient ones; the only really doubtful one is ether, which can easily be dispensed with. We only need, then, an anæsthetist who can be relied upon to give smooth induction and maintenance, and who will promptly deal with sputum should occasion arise; the postoperative stage is then unlikely to be troublesome. Even if thereafter the patient does not do well, the case against inhalational anæsthesia has by no means been proved. The prognosis at all stages of tuberculosis is most uncertain, and the technique of the anæsthetist may become the scapegoat.

I would like to emphasise—as have others—that it is not the drugs that matter, but the anæsthetist. I would suggest that "an earnest if inexperienced registrar" is a most unsuitable anæsthetist for this type of case.

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[1] The Marihuana Problem in the City of New York. New York, 1944.

These patients have often had years of experience of doctors and are quick to distinguish one who is experienced from one who is not. The hysteria which followed the intradural injection may have originated in the preoperative visit in the ward.

These principles apply equally to emergencies at night and during the weekend. Registrars are in sole charge in many hospitals, and however well they work a consultant should be able to do better on some occasions. There should therefore always be a consultant available for difficult and serious cases. The case mentioned by Dr. Mushin would come into this category. Had she been anæsthetised by a more experienced person the serious sequelæ would probably not have occurred.

Portsmouth. H. B. C. SANDIFORD.

TREATMENT OF SCARLET FEVER

SIR,—I share Dr. Krarup's surprise (March 29) that there exist doctors who do not use penicillin in the treatment of "scarlet fever." I am always bewildered when I hear of cases of "scarlet fever" being admitted to hospital, of isolation of contacts, of stovings and fumigations.

When I qualified ten years ago—in England, I hope Dr. Krarup will note—I had already been taught that at least thirty different types of group-A (Lancefield and Hare) streptococci had been isolated by Griffith from cases of "scarlet fever," and that any streptococcal throat infection, whether due to organisms which produced an erythrogenic toxin or not, might be clinically as serious, and as liable to immediate and late complications, as "scarlet fever."

Accordingly I have never diagnosed, nor used the term, "scarlet fever," nor yet notified a case. I often see "scarlet fever" in association with acute tonsillitis; I have seen it when the only lesion is a boil on the buttock, or when a slight purulent infection of a laparotomy scar has been the cause.

As the use of the term still causes dismay to patients, nurses, and all school authorities, is it not high time that tonsillitis (with or without a "scarlet fever" rash) replaced the term "scarlet fever"?

Hildenborough, Kent. C. GLAISHER.

WHAT SHOULD THE NURSE BE TAUGHT ?

SIR,—As matron of a nurse-training school, I read the letter from Dr. Cropper and Dr. Houghton (April 5) both with interest and with dismay.

I am fully in agreement with their desire for a simplified theoretical syllabus, and am glad to see the revised State examinations giving greater prominence to practical nursing, that essential of the training which theoretical work can augment but never replace.

The first part of the letter, however, caused me great concern. Many senior members of the nursing and teaching professions are greatly disturbed by the growing number and wide acceptance of schemes whereby young people from 15 years of age are employed in hospitals. From a purely material point of view these schemes are a heavy financial burden upon our already overtaxed health service, and are already tending to defeat their own ends.

A number of girls, attracted by the salaries offered and by the excitement of working in hospital, and commonly under the delusion that they are starting their nursing career in the best possible way, are leaving school earlier than they would normally have done, thus creating the gap between school and training which the cadet course is intended to fill. When training eventually starts, the wastage among these candidates is, in my experience, very high—from lack of basic education, from disillusionment when confronted with genuine nursing duties, or from sheer weariness and loss of enthusiasm after so long a period of institutional work. Because of this, I have lost more than one promising student when half-way through her training.

Worst of all is the danger of permitting junior nurses to do any work in a hospital when at present there is no means of ensuring that the recommended conditions of service are enforced. Although in recognised cadet schemes every care is taken that the approved conditions are strictly adhered to, there are far too many hospitals where, for lack of other staff, young girls are regularly employed in actual nursing duties—not only on day but on night duty.

Years ago child-labour was abolished in the mines and the factories of this land. In our twentieth-century health service children are engaged in nursing the sick. Can we of all people, members of the medical and nursing professions, view such a situation with equanimity?

Addenbrooke's Hospital,
Cambridge.
L. J. OTTLEY
Matron.

ARTIFICIAL RESPIRATION

SIR,—In answer to Dr. Hicks (April 5), I did not mean to condemn any method of resuscitation, but I objected to the suggestion that Schafer's method should be officially replaced by Nielsen's.

I adhere to my opinion, not only because thousands have been trained to carry out the Schafer method efficiently, but because it is the only method which makes full use of the diaphragm. At the same time it allows other methods, such as Nielsen's, to be used if help is at hand. If the value of the diaphragm is to be disregarded, the rocking stretcher must also retire to the background.

Only four days ago, a fellow practitioner witnessed my resuscitation of a patient with acute asphyxia by Schafer's method, along with the principle of the rocking stretcher. The heart-sounds were inaudible with the stethoscope; and it was exactly twenty minutes before the welcome grunt was heard, and another five minutes before we could say that breathing was established. In this case, as in others which I have experienced, the regular diaphragmatic movements, in my opinion, served to stimulate contraction of the heart.

I consider therefore that Schafer's method should be retained. If advantage is to be taken of the value of the diaphragm, either the Schafer or the rocking-stretcher method should be used; but these may be combined with other methods.

Hemel Hempstead. GILBERT BURNET.

SELF-DEMAND FEEDING OF INFANTS

SIR,—I have read with interest the article by Professor Illingworth and Dr. Stone (April 5) on the merits of self-demand feeding of infants. If it serves to draw attention to the need to avoid a rigid routine in baby-feeding the results will prove most valuable. On the other hand, I think it would be a mistake to create the impression that any routine in baby-feeding is undesirable. I think that some confusion may arise as a result of the terms used. The authors refer at the beginning of the article to the benefits of an "elastic feeding schedule" and later refer to their results as showing the advantages of "self-demand breast-feeding." I think it is important to distinguish between these two phrases. Most mothers welcome some guidance regarding the frequency and duration of feeds, and they will find an elastic feeding schedule a help. On the other hand, they are likely to get into difficulties if they are led to think that everything can be left to Nature and that baby can be fed at any time of the day or night.

Babies as a rule naturally get into fairly regular habits, and if the mother without being in the least rigid can help to form habits that involve feeding baby at reasonable hours she will save herself a lot of trouble to the benefit of both herself and her baby.

L.C.C. Divisional Offices,
128, Brook Drive, London, S.E.11.
W. H. S. WALLACE.

HYPERTHYROIDISM AND PEPTIC ULCER

SIR,—I have read with interest the article (April 5) by Dr. Morton Gill and Dr. Walton, who record three recent cases illustrating the simultaneous occurrence of these rarely associated conditions. In each of their three cases the abdominal symptoms ceased, and remained absent so long as the patients were observed, as soon as the hyperthyroidism was controlled, whether by thiouracil or operation.

The same happy result has followed in my own experience.[1] In several cases of thyrotoxicosis that have come under my care, in which abdominal symptoms similar to those of peptic ulcer have been present, a permanent cure of the abdominal symptoms has followed subtotal thyroidectomy. Indeed, the cure has been so immediate, complete, and permanent, that I have wondered whether the abdominal symptoms were not part of the thyrotoxic syndrome, in spite of the positive X-ray findings. However this may be, I believe that in all such cases the thyrotoxicosis should be treated first, in the confident hope that the abdominal symptoms will cease.

Bradford. PETER MCEWAN.

REDUCTION OF STRANGULATED INGUINAL HERNIA

SIR,—My brief article on the reduction of strangulated hernia [2] has aroused more interest and comment than I expected.[3–5] May I summarise again the treatment which I described for cases diagnosed within twenty-four hours of onset (excluding Richter's hernia):

1. Very high blocks (2 ft.) under foot of bed.
2. Morphine gr. $^1/_2$ for adults (not gr. $^1/_4$).
3. Cold compress to groin and scrotum.
4. General warmth to patient.
5. Flexion of both legs at hips and knees with three pillows (it is necessary to put two pillows at the head of the bed to prevent the patient's head from going through the bars as the bed's slope is steep).

Dr. Marcus tried the method with success in the patient's home. All my cases have been treated *in hospital*. It may be permissible to make a trial of this method at home while making arrangements for admission, but to defer these arrangements in the hope of success is unwise and would legitimately be criticised by the surgeon who had to operate when the method failed. In remote country practice where transport and communication are difficult long delay may be inevitable, and postural treatment while awaiting admission to hospital may reduce many strangulated herniæ and tide the patient over a serious emergency.

The likelihood of reduction within a given time is important, because of the risk of gangrene. In my recent series (January to December, 1951) the method was tried in 55 cases; 40 herniæ were reduced and 15 were not.

By the end of 1 hour	12	(*22%*)	were reduced
,, ,, ,, ,, 3 hours	18	(*33%*)	,, ,,
,, ,, ,, ,, 6 ,,	31	(*56%*)	,, ,,
,, ,, ,, ,, 9 ,,	40	(*73%*)	,, ,,

In 3 cases reduction was almost complete when the limit of eight hours was reached and they were left for some minutes longer. The successful-reduction rates in my two series bear a remarkable similarity—34 out of 47 (72%) in 1949 and 40 out of 55 (73%) in 1951.

Mr. Monro made a very shrewd guess that in perhaps half the cases the herniæ might be reduced if postural treatment were undertaken in hospital for four hours, during which preoperative intravenous saline might be given to counteract the effects of vomiting. The actual figure at four hours was 47%.

Mr. Macfarlane viewed the procedure with reserve and some scepticism. Considering his misfortune in striking a double-loop hernia of Maydl type, it is not surprising that he feels caution is necessary; and I agree with him. From my experience of many thousands of herniæ I find a Maydl double-loop hernia occurs in about 0·5%, and it is very dangerous. I saw one such case last year when more than twenty-four hours had passed since symptoms began. Two large loops were non-viable and the patient died after an extensive resection.

In the 26 patients operated upon I took particular note of the apparent cause of the strangulation. Half the herniæ seemed to be constricted at the external ring and half at the neck of the sac. Where strangulation is caused by a fibrous ring round the neck of the sac, reduction by posture seems less likely than when the external ring alone is responsible for the constriction. Only a small proportion of herniæ repaired by routine operation show a well-developed fibrous ring at the neck (perhaps 10%). In 50% of the herniæ which were not reduced by posture the constriction was caused mainly by a well-developed neck. This unduly high proportion suggests that a constricting neck is a frequent cause of failure of postural treatment. The pressure of a fibrous neck is unaffected by morphine; on the other hand, muscular spasm in external-ring strangulations is much decreased by heavy sedation. I gained the impression that most patients in whom a tight neck is found are young men aged 20–30 who have suffered from hernia for only six months to a year. Their strangulated herniæ require the most careful watching and seem less likely to reduce than those of older patients with a longer history.

Maingot [6] gives the mortalities for first-day and second-day cases as 6% and 30% respectively. The corresponding figures in my two series were approximately 3% and 33% in 1949 and 2% and 33% in 1951. An analysis of my 1951 results is given in the table.

RESULTS OF 66 CASES OF STRANGULATED HERNIA (1951)

Type of case	No. of cases	Treatment	Deaths	Mortality
Strangulated hernia under 24 hours; reduced ..	40	Postural	Nil	Nil
Strangulated hernia under 24 hours; posture failed; gut viable	13	Herniorraphy	1	8%
Strangulated hernia under 24 hours; posture failed; gut gangrenous	2	,,	Nil	Nil
Strangulated hernia over 24 hours; immediate operation (excluding Richter's hernia).. ..	6	,,	2	33%
Strangulated Richter's hernia; immediate operation	5	,,	Nil	Nil
Total	66		3	4·5%

Of the 55 patients treated posturally in 1951, 1 died; there was also 1 death in 1949 among 44 cases similarly treated. In the whole series, there were 2 deaths among 47 cases in 1949 (4·3%) and 3 deaths among 66 cases in 1951 (4·5%).

I would *again* stress that a strangulated Richter's hernia ("bubo type") should be operated upon at once, because of the high risk of early gangrene. In 3 of the 5 patients I treated in 1951 gangrene was present at operation.

Not all those patients successfully treated by posture have yet been operated upon, but there have been no deaths among those who have.

Complications after postural reduction are few, as opposed to the frequent troubles which follow immediate operation—e.g., retention of urine and chest infections. Such complications are attributed to the poor initial condition of the patient and to the lack of time for adequate preoperative preparation in such a serious emergency. These considerations must be kept in mind when comparing techniques. Patients usually seek treatment at an earlier stage in England than in Africa, and I feel that my figures could easily be improved upon at home. I look forward to the appearance of such figures because I have little doubt that a method which proves its worth over many years is certain to be widely adopted despite some opposition at first.

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[1] McEwan, P. The Clinical Picture of Thyrotoxicosis. Edinburgh, 1948; p. 52.

[2] Bowesman, C. *Lancet*, 1951, i, 1396.

[3] Marcus, M. *Ibid*, ii, 543.

[4] Macfarlane, D. A. *Ibid*, p. 685.

[5] Monro, A. K. *Ibid*, p. 839.

[6] Maingot, R. Abdominal Operations. London, 1948 p. 875.

Kumasi, Gold Coast. C. BOWESMAN.

RADIOLOGICAL INVESTIGATION

SIR,—I have read with interest and with amusement over the last few years Dr. Brailsford's polemics against the supposed sins of the clinicians. If all his facts were well founded one might forgive him; but such is not the case. In his most recent paper (April 5) he says: "The fact that young adults die from undiagnosed pulmonary tuberculosis is not due to failure to radiograph them, but to bad clinical examination." When any medical man makes such a statement it is difficult to believe that he has any real clinical experience of the subject on which he writes. In a recent survey on minimal pulmonary tuberculosis, I discovered that in over 60% of the cases there were no symptoms and in over 70% there were no signs. These features have been borne out by other workers.[1] I quite agree with Dr. Brailsford that one can obtain signs and symptoms in pulmonary tuberculosis, but I can assure him to wait for these is to court disaster.

One of the curious things about the majority of radiologists (on which Dr. Brailsford fails to comment) is the infrequency with which they attend necropsies. The result is that, in tuberculosis of the lungs in particular, their interpretation of radiological findings in pathological terms is particularly confusing. Many still use such terms as "Assmann's focus," "Simon's foci," and "mottles" for caseous nodules of varying size. Eponymous names beloved of an earlier generation of physicians only serve to confuse.

The radiologists often use the term "productive lesion" in regard to pulmonary tuberculosis. I hold that this term can only have any real meaning when applied by the pathologist to a state of affairs found with the aid of a microscope.

There is no doubt that, where the more difficult techniques of radiology are concerned, the radiologist is often of great help to his colleagues. But the ultimate responsibility in regard to treatment lies with the clinician. He is the only person who can assess as a whole the laboratory and the clinical findings.

Speke, Liverpool. PETER O. LEGGAT.

RUBBER TUBING AS A CAUSE OF INFUSION THROMBOPHLEBITIS

SIR,—Dr. Handfield-Jones and Dr. Lewis (March 22) have, by their investigation of thrombophlebitis during intravenous-drip therapy, done much to prevent mistrust by the surgical and medical staffs of intravenous solutions prepared in dispensaries and the defensive mistrust by the pharmacist of techniques in the wards.

As a result of its prevalence at this hospital a rather similar investigation was carried out. Possible factors, such as the water and materials used in the solutions and the detergents and procedures adopted to cleanse the bottles and caps, were changed one at a time and the solutions traced by batch numbers to the wards. We achieved no improvement with any of these changes.

A small number of drip-sets were intercepted before reaching the wards, and these were stripped down to their components, subjected to extensive cleansing procedures, reassembled, and sterilised. The dye was omitted from the outer 'Cellophane' wrapping. A small drop in incidence did occur but was perhaps not reliable as little more than a dozen sets were treated this way, because the process is time-consuming.

Our figures set out as in table II of the article by Dr. Handfield-Jones and Dr. Lewis were as follows:

Blood		Saline and/or blood		Glucose, glucose-saline, &c.		Total	
No.	% reaction	No.	% reaction	No.	% reaction	No.	% reaction
10	2	11	1	31	14	52	32

These figures are very similar to those obtained with the Oxford tubing B. Perhaps this tubing is in use at the Barnet depot from which we receive our sets.

Finally we noticed here that quite frequently the reaction did not occur until perhaps 24 hours after the cessation of therapy. This occurred in all wards so was probably not due to after-dressing technique. It might suggest that the causative substance is retained by the tissues in the immediate vicinity of the puncture until a critical time × concentration is reached. The figures recorded in table I of the article could be explained in this way.

Meanwhile figures showing the incidence in a hospital where translucent tubing is exclusivley used would be of considerable interest.

Lister Hospital,
Hitchin, Hertfordshire. JOHN C. SMITH.

ANTIBIOTICS IN AMŒBIASIS

SIR,—I have read with great interest your annotation of March 29. It seems to me unlikely that any combination of antibiotics or amœbicidal drugs will prove successful against amœbiasis without the concomitant application of strict food hygiene and other public-health measures, such as the control of water-supplies, elimination of insects that transmit the causative agent, and control of cyst excretors.

Bargen[1] believes that in the general population of the U.S.A. the incidence of infection with *Entamœba histolytica* is 5–10%. Anderson et al.[2] estimated that 17% of the personnel of a Memphis Hospital were infected with amœbæ. In tropical countries the incidence of infection may be as high as 70–80%. My own figures from an investigation of 300 new entrants to industry in Central India showed the cyst-passer rate to be 70%. It is difficult to agree with Albright and Gordon's[3] observation that there is no such thing as a healthy carrier of amœbiasis, and that the carrier has active disease. In fact a fair proportion of cyst passers are symptom-free; and hence these cannot be filtered out from food-handling trades without careful and repeated stool examinations.

Reinfection seems to be the main problem.[4] I have been very much impressed with the freedom from symptoms of a few patients with chronic amœbiasis who took a course of aureomycin on coming to England from India nearly a year ago, whereas previously they used to "relapse" after every course of treatment. In India local habits contribute to the ease of reinfection. Post-defæcation ablution is responsible for a high rate of potentially infective fingers, and the custom of preparing and eating food with fingers naturally adds to the ease of spreading infection and to self-reinfection. I therefore feel that attention should be centred on the control of these factors. So far as treatment is concerned, the effect of aureomycin in individual attacks is highly satisfactory, but in the long run it is very poor under conditions favouring reinfection.

London, W.2. S. L. MALHOTRA.

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1. Phelps, P. S., Edson, R. C., Taschman, M., Amberson, J. B. *Conn. med. J.* 1943, 7, 19. *J. Mt Sinai Hosp.* 1945, 12, 724. *Conn. med. J.* 1945, 9, 333.

1. Bargen, J. A. *J. Amer. med. Ass.* 1951, 145, 785.
2. Anderson, H. H. *Amer. J. trop. Med.* 1948, 28, 373.
3. Albright, E. C., Gordon, E. S. *Arch. intern. Med.* 1947, 79, 253.
4. Malhotra, S. L. *Ind. med. Gaz.* 1949, 84, 96.

Medicine and the Law

The Royal College Wins

BY reversing a decision of 1899 the House of Lords has established that the Royal College of Surgeons is in the legal sense a charity. The college will consequently benefit by receiving the endowment fund set up by Lady Bland-Sutton's will; presumably it will also have the advantage in future of the exemption from income-tax which the 1899 decision refused.

The charter of 1800 recited that the object of the college was "the due promotion and encouragement of the study and practice of the art and science of surgery." In 1899 the Court of Appeal held that the income of the college was not "for the promotion of science" (within the words of the relevant statute) because the promotion of the interests of practising surgeons was one of the main objects. The House of Lords, by a majority of four to one, has now taken a different view of the words in the charter. "Study" and "practice," said Lord Morton of Henryton, embody two ideas—research in the laboratory, and the practical experience which can be gained only by using surgical implements upon human or other bodies. The promotion of the interests of surgeons, emphasised in the 1899 decision, was, he thought, no more than an incidental, though an important and perhaps a necessary, consequence of the work of the college in carrying out its main object. Lord Cohen, in a dissenting judgment, felt that the disciplinary and "defence" activities of the college were something more than secondary and consequential. He therefore regarded them as not merely ancillary to a main charitable object but as non-charitable activities which prevented the college from being regarded as a charity in law. His view did not prevail.

The Bland-Sutton litigation has had a curious course. The will created a trust fund for, amongst other things, the maintenance and benefit of the Bland-Sutton Institute of Pathology, then part of the Middlesex Hospital medical school. If the hospital became nationalised or by any means passed into public ownership, the fund was to be transferred to the Royal College of Surgeons. The testatrix died in 1943: the hospital was transferred to the Minister of Health on July 5, 1948, under the 1946 Act. Mr. Justice Danckwerts held that the hospital had not been nationalised within the meaning of the will.[1] The Court of Appeal reversed him, but held that the gift over to the college was invalid because it was contrary to the legal rule against perpetuities unless the college were a charity.[2] The Court of Appeal could not hold the college to be a charity because in 1899 it had taken the opposite view. Now the House of Lords (not being bound by the Court of Appeal's judgment of 1899) has decided that the hospital was nationalised and that the college is a charity after all.

Lord Morton rendered a great service in drawing attention to the fact that the legal definition of a charity primarily depends upon words in the preamble to a statute of Queen Elizabeth I, of which statute every word except the preamble is repealed. It is high time, as he observed, that the Legislature re-wrote the law. Perhaps the Lord Chancellor's Law Revision Committee could be asked to undertake the task. Meanwhile what is the Inland Revenue doing about the money withheld—wrongly, as it is now clear—since 1899?

A Fatal Misunderstanding

After investigating a regrettable accident at a hospital recently, a coroner's jury returned a verdict of death by misadventure, but added a rider that there had been "a considerable amount of neglect" (*Birmingham Post*, March 29).

A boy, aged 11, entered hospital for a minor operation. The doctor who administered the anæsthetic inserted a pad of yellow-dyed bandage in the patient's mouth. She had, immediately afterwards, to anæsthetise another patient in an emergency case. She left the boy in charge of another anæsthetist who, she felt satisfied, was aware that the patient's mouth was "packed." The second doctor, when the boy's operation was completed, looked in the patient's mouth and inserted her fingers but found nothing. She took out the tube, inserted an airway, and considered the boy's breathing to be quite normal. The boy died and a pad of gauze was recovered from his throat.

Prof. J. M. Webster, giving evidence at the inquest, said that death was due to asphyxia; the operation had been skilfully performed; there was no sign that the anæsthetic had been given in excessive quantity or unskilfully: resuscitation had been properly attempted. Professor Webster said it was imperative that some method of marking should be adopted. He recommended the use of adhesive plaster, some harmless marking of the skin, or even the use of a thin type of plug which would be allowed to hang from the corner of the mouth. He criticised the practice of an anæsthetist changing patients in the course of a case. The jury expressed full agreement with these observations, and the chairman of the hospital management board gave an assurance that everything possible would be done to prevent a recurrence of such an incident.

The Deceased Reappears

The textbooks record many grounds upon which an inquest has been quashed. Sometimes it was because the verdict was unintelligible or inconsistent or insufficient, or because there had been no view of the body or for some merely technical reason. Most solid ground of all, and probably the rarest, is the reappearance of the supposedly dead man.

On April 7 the Divisional Court quashed an inquisition on an inquest held last August in the West (Chester) Ward of the County of Durham. The body, found drowned in the River Tyne, had been alleged to be that of a Mr. Septimus Parker. Two months later Mr. Parker turned up alive. It is now suggested that the body was that of a Mr. J. W. Bullock-Anderson.

The Divisional Court acted under section 19 of the Coroners (Amendment) Act, 1926. This (without prejudice to the common-law powers of the High Court or the powers, under section 6 of the 1887 Act, on application on behalf of the Attorney-General, to order the holding of an inquest where there has been fraud or other irregularity) allows the Court to quash an inquest and order the holding of a fresh one where the discovery of new facts or evidence makes it "necessary or desirable in the interests of justice." A coroner cannot on his own authority hold a second inquest.

It may be added that quashing does not necessarily imply wrongful conduct on the part of the coroner. He may himself become aware of new facts or evidence which make him dissatisfied with the inquest already held; and he may himself set in motion the proceedings to obtain the High Court's intervention.

Fatal Fall Ascribed to Epilepsy

The claim for damages in Cork *v.* Kirby Maclean Ltd. seemed a simple one. Albert Cork, a painter, was engaged in painting the roof inside his employers' factory at a height about 23 ft. above the floor. The Building (Safety, Health and Welfare) Regulations of 1948 require that, if anybody is liable to fall more than 6 ft. 6 in. from a working platform and if "material" (such as a painter's bucket and brushes) are on the platform, then the platform must be at least 34 in. wide. They also require suitable guard-rails of adequate strength

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1. See *Lancet*, 1950, ii, 155.
2. *Ibid*, 1951, i, 405.

and toe-guards of a sufficient height. The platform on which Cork had his "material" was about 27 in. wide, and no guard-rails or toe-guards were provided. He fell from the platform and was killed. His death could have been due to his employers' breach of the regulations; the law placed upon his employers the burden of proof to the contrary.

Their defence was an allegation that he suffered from epilepsy and had omitted to tell them of it. When, they said, he entered their employment (three days before his death), they explained to him that his job would involve climbing ladders and working on a platform. He never told them that he had suffered from epileptic fits for ten years, that he had received medical treatment for epilepsy only ten days before his death, and that his doctor had advised him on no account to climb ladders or work at a height. They contended that his fall was due to an epileptic fit or fainting attack and that his death was caused by his own negligence in undertaking work against which he had been warned. Mr. Justice Donovan said that the object of the regulations was to prevent workmen from falling off working platforms; a man might fall because temporarily he lost control of his bodily movements whether through carelessness, illness, or unconsciousness. If he fell because of unconsciousness, employers who had broken the protective regulations would not be absolved. To escape liability they must prove that the deceased would have fallen off the platform even if guard-rails and toe-guards had been provided. That, said the judge, must be mere guesswork; there was an obvious chance that the rails and boards, if provided, might have saved him. The consequences of the employers' breach of the regulations could not depend on whether the deceased did or did not disclose all or some of his infirmities. Judgment was given for the widow.

In the course of giving judgment His Lordship remarked, somewhat cryptically, that he felt he must be on his guard against the possibly insidious effect of the word "epileptic" upon the mind. Perhaps he meant that, if the deceased fell by reason of overbalancing, the legal result was the same whether the cause of the overbalancing was epilepsy or mere giddiness.

Parliament

The Bill Still in Committee

ON April 8 at the resumed committee stage of the National Health Service Bill, Mr. H. L. MARQUAND moved the first of 15 amendments to exempt surgical appliances issued through the hospital service from the proposed charges. In response to public feeling the Minister had already said that he would levy no charge on hearing-aids and had limited the charges to four types of appliances. As a result the Minister could now only hope to save £250,000 from this part of the Bill. Mr. Marquand felt there could be no question of abuse when the appliances were ordered through the hospital service and their quality and type controlled by the Ministry of Pensions.

Mr. H. F. C. CROOKSHANK reiterated his assurance that only four types of appliances would carry a charge—surgical boots and repairs, abdominal supports, elastic hosiery, and wigs. He agreed that £250,000 was not a very large sum, but with the other items it enabled him to keep the general cost of the service below the ceiling. Some members wanted some things, such as hearing-aids, specifically excluded. He thought that was just the kind of thing to leave to regulatory powers, and instead of putting a string of exemptions into the Act he asked that the word "appliances" should be allowed to stand.

A SMALL SUM

Mr. ANEURIN BEVAN pointed out that the total cost of the appliances was £4 million, and the total hospital expenditure £230 million, while the charges on appliances would bring in about £250,000. It was hard to listen to these figures without coming to the conclusion that the Government were concerned primarily with breaching the principle of free service rather than collecting revenue for the State. The only reasonable argument for the charges—the ceiling—was already gone. Or did Mr. Crookshank really intend to find the £10 million for the general practitioners for this year within the ceiling?

Mr. CROOKSHANK interrupted to say his objective had been to keep below the £400 million ceiling. When the Danckwerts award came along it was on a larger scale than anyone expected, but that was no reason why previous efforts to keep under the £400 million should be denigrated.

Mr. BEVAN persisted that to collect money for appliances while paying another £10 million a year to the doctors was to create a curious kind of conflict within the service. And it was all the worse because of the smallness of the sum involved.

Mr. ENOCH POWELL thought it fallacious to argue that because a public debt of honour had to be paid there was no longer any need to restrain the tendency of the total cost of the service to rise. It was also a fallacy to suggest that whenever a patient paid a charge he was paying for the doctor: you might just as well say he was paying for the nurses and for the beds in hospitals, Mr. Powell declared. It had been suggested that a charge on appliances might encourage patients to buy quack appliances, but the cost of the charges would not exceed half the cost of the appliance and he believed it unlikely that a quack appliance could be provided for less. Mr. W. GRIFFITHS pointed out that there already was concern about the enormous growth in sales of spectacles in the chain stores.

Mr. A. BLENKINSOP asked whether the almoners were to be forced back into their monetary collections, or whether new staff was to be appointed to collect these charges. He suggested that administrative expenses might easily amount to £100,000. But Mr. CROOKSHANK thought that administrative costs would be minute, for only about 800 appliances were issued daily over the whole country. The amendment was lost by 291 votes to 273.

The next 14 amendments, all concerned with the exemption of different appliances, were taken together. By agreement the House only divided on 4, all of which were lost.

REDUCED CHARGES

Mr. F. MESSER moved two amendments limiting the charges for appliances to a quarter of their cost and for prescriptions to 6*d*. He wished to write these maxima into the Bill so that we should understand the burden people would be called on to bear. It was true that needy people could go to the National Assistance Board for help but in his view working people were too independent to go readily. The implied application of a means test was an indignity. Was it our conception of civilisation that someone should have to bear the full burden of a physical handicap? Should we not pool our resources to help them?

Many people were living happier lives because of the service, but there was need for economy. Indeed he believed more money could be saved than would be gained by this Bill. But it was unmoral to save money at the expense of those least able to afford it. He did not grudge the G.P.'s their increase, but he would like to see the standard of general practice improved. With a higher standard we might need fewer hospital beds. One section of the medical profession, he declared, was not doing too badly out of the service. Some former full-time specialists at municipal hospitals were now working part-time on a sessional basis. Men who in the old days got £1500 a year now got £3000 or £4000, and expenses free of income-tax. Mr. Messer believed there was opportunity here to save money. He also considered that the Treasury's method of controlling hospital finance led to waste. He feared that when people had become familiarised with paying for something, further charges would be added until we had destroyed "the finest monument to the ability of the people of this country to build for themselves an instrument for the benefit of all."

Dr. **BARNETT STROSS** said the Minister had suggested that the £50 million spent on drugs was evidence of abuse. But might it not also be evidence of a reduction in self-medication? Although the amount spent on self-medication today was about the same as before the war—£30 million—owing to rising costs the actual amount of medicines bought had been halved.

Miss **PATRICIA HORNSBY-SMITH** maintained that it would be more appropriate to debate these charges when the regulations were before the House. Both amendments were rejected.

Miss **IRENE WARD** moved an amendment that foreign nationals should be charged the full cost of appliances. She agreed it might be difficult for a doctor called upon to give emergency treatment to differentiate between a foreign national and a nationalised British subject. She had therefore excluded prescriptions from her amendment. But she could not believe it was beyond administrative wit to devise a way of imposing a charge on foreign nationals for appliances. Mr. **CROOKSHANK**, however, had difficulty in interpreting the phrase "nationals of foreign countries," and he saw no easy way of identifying these people. The abolition of identity cards, which he welcomed, had made the situation more difficult. He doubted if there was any great abuse. The amendment was defeated.

COLLECTION OF CHARGES

At the resumed committee stage on April 9 Dr. **STROSS** moved an amendment that no doctor should be required to make or recover any charge. In hospitals, he assumed, charges would be paid at the dispensary, but what would happen at clinics—especially V.D. clinics—where personal attention and secrecy were important? Though the clause under discussion dealt only with hospital services he foresaw further difficulties among rural doctors who did their own dispensing, some by tariff and some by capitation fee. What was particularly objectionable was the degradation of the status of the doctor and the spoiling of the relationship between him and his patient.

Dr. **A. D. D. BROUGHTON** said that other amendments had been trying to protect the patient; this one was to protect the doctor. The N.H.S. had divorced the doctor from trade and allowed him to give all his time to his patients. He believed the doctor should be adequately paid and allowed to concentrate on his professional work. Collecting shillings would be a degrading imposition. A doctor could not give a bottle of medicine to an old-age pensioner, a child, or an emergency case until he had extracted a shilling.

Miss **HORNSBY-SMITH** said that the possibility that a doctor would have to collect charges from outpatients was so remote that no representation on the clause had been made by the profession. Arrangements with rural doctors were being worked out, and she believed that arrangements would be reached satisfactory to both sides. She did not want to enter into an argument on controversial points while these negotiations were proceeding smoothly. Patients at V.D. clinics would by regulation be exempted from the charges. The hospitals already had machinery, provided under previous legislation, to collect charges for repairs to appliances and in specialist hospitals for dentures and spectacles. She thought the H.M.C.s could therefore make arrangements for the collection of the charges proposed under this Bill. The amendment was rejected by 284 votes to 263.

Mrs. **E. M. BRADDOCK** moved an amendment that no H.M.C., board of management, or board of governors be required to make or recover any of these charges; otherwise she believed doctors might well keep a patient in hospital for an extra couple of weeks instead of referring him to the outpatient department. This might add considerably to hospital costs. If the Minister would continue to put his trust in the medical profession, she believed he would probably save more than he hoped to collect in these charges. Mr. **CROOKSHANK** pointed out that the amendment was a wrecking amendment, for the bodies named were the only people who could set in motion the machinery for collecting the charges. The amendment was defeated.

Having reached line 9 of the Bill after three days' discussion the committee adjourned until April 21.

National Insurance

On April 8 Mr. **OSBERT PEAKE**, the Minister of National Insurance, announced that the Government had decided to introduce at the earliest possible moment a Bill to increase National Insurance benefits and pensions on the lines indicated by the Chancellor of the Exchequer in his Budget. These proposals were:

(1) an increase in the rate of family allowances from 5*s*. to 8*s*. a week.

(2) an increase in National Insurance benefits, including unemployment, sickness, and widows' benefits, and retirement pension from the present figures of 26*s*. single and 42*s*. married to 32*s*. 6*d*. single and 54*s*. married. These higher rates of retirement pension would be paid at the existing ages of 65 for men and 60 for women. They would also be made available to existing pensioners in Great Britain whether they reached pension age before or after Oct. 1, 1951.

(3) an increase in the basic rate of industrial injuries benefit from 45*s*. to 55*s*.

These proposals would for the first full year cost, for family allowances which come out of the Exchequer, about £37 million, and for National Insurance and Industrial Injuries benefits, which come out of the Insurance Funds, about £60 million and £3 million respectively. He hoped to bring the new rates of retirement pension into operation at the end of September, family allowances by the beginning of September, and other improvements such as those of sickness and unemployment towards the end of July. The new rates of contribution would become payable in October.

National Assistance

The same day Mr. Peake laid before Parliament draft regulations[1] to increase the allowances granted to persons in need by the National Assistance Board. The proposed increases, to be made on June 16, are:

(1) the scale rate (i.e., the weekly amount provided for requirements other than rent) for a married couple, which at present stands at 50*s*., is to be increased by 9*s*.

(2) the scale rate of 26*s*. for a single adult is to be increased by 5*s*. The special scale rates for blind and certain tuberculous persons are being increased by rather larger amounts.

(3) the scale rates for dependent children under 16 years of age, ranging from 9*s*. 6*d*. to 13*s*. 6*d*., are to be increased by amounts varying from 1*s*. 6*d*. to 2*s*. 6*d*.

These increases, it is estimated, will cost about £25 million a year, and they may cost more because a number of people who cannot at present qualify for assistance or have not so far applied may do so after the introduction of the new scales. The annual saving on assistance which will result from the increases in retirement pensions and other insurance benefits and family allowances is likely to be substantial, but cannot be estimated until the Government's proposals are published in more detail.

Care of Senile in Scotland

In the House of Commons, on April 8, Mrs. **JEAN MANN** was granted leave to bring in a Bill to permit in Scotland the reception into and maintenance in mental hospitals and similar institutions for care and attention senile persons without certification of insanity or lunacy. She said that the Bill would not have been necessary if 20 years ago this problem had been approached in the correct way. At that time a leading mental specialist in Scotland urged local authorities to make provision in mental institutions for an ageing population. At present certification was the only way in which aged people could obtain a bed and this caused distress to their families. It could not be expected that this problem would diminish; indeed it was increasing. She sought nothing more in this Bill than to remove the stigma.

Mr. **DAVID LOGAN** opposed the Bill because what it proposed was the wrong procedure. Unless segregation of the aged from the certified was intended the Bill would only continue an existing evil. We wanted to get rid of the system of aged and infirm people being placed in mental institutions. The stigma was created because we had not a proper place for aged senile people.

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[1] Draft National Assistance (Determination of Need) Amendment Regulations, 1952. 2*d*.

QUESTION TIME

Cost of N.H.S. Prescriptions

Replying to Dr. A. D. D. BROUGHTON, Mr. H. F. C. OOKSHANK said that the approximate average cost of a tional Health Service prescription in the second half of 1948 s 2*s*. 8½*d*. In the years 1949 and 1950 it was 3*s*. and 3*s*. 2½*d*. pectively. Complete figures for 1951 were not available, but average cost was estimated to be 3*s*. 8*d*. No figures were ailable for 1952. The number of N.H.S. prescriptions pensed in England and Wales in January in 1949, 1950, 51, and 1952 respectively were 18,343,000, 19,892,000, ,917,000, and 20,799,000.

Fluorine and Dental Decay

In answer to a question Mr. CROOKSHANK said that a scientific ission was at present in the United States on behalf of the itish Government, studying the diminution of dental decay hieved by the addition of fluorine to the drinking-water pplies.

Consumption of Welfare Foods

Mr. FREDERICK WILLEY asked the Minister of Food the rcentage uptake of the various welfare foods.—Major WILYM LLOYD GEORGE replied: About 97% of those titled to obtain milk or National Dried Milk under the lfare foods service do so. The quantities of the vitamin pplements taken up in 1951 expressed as a percentage of e full entitlement are as follows: orange juice 30%; cod-er oil 27%; vitamin tablets 33%.

Doctors' Remuneration

Replying to Mr. HASTINGS, Mr. CROOKSHANK said that the erage number of principals providing medical services under rt IV of the National Health Service Act in the year ended arch 31, 1951, was 17,717. They were not paid salaries, it their total remuneration for such services, including the lue of the Exchequer superannuation contributions, was 3,506,262. This represented an average of £2456 per doctor, it of which he had to meet his professional expenses. In swer to a further question, Mr. Crookshank said that in the me year the average payment on an annual capitation fee of s. was just under 16*s*. 5*d*.

In answer to a similar question Mr. JAMES STUART stated at the average number of principals in Scotland was 2415. heir total remuneration before deduction of superannuation ntributions (but excluding the Exchequer superannuation ntribution of £253,299) was £5,220,544. This represented average of £2162 per doctor.

Demand for Dentures

Replying to a question Miss PATRICIA HORNSBY-SMITH said at from the beginning of the National Health Service to arch 31, 1950, the numbers of full dentures (upper or lower) d partial dentures supplied were of the order of 5 million and ½ million, respectively. For the year April 1, 1950, to arch 31, 1951, the corresponding approximate figures were ,780,000 and 1,150,000, and for the nine months ended ecember 31, 1951, 2,210,000 and 780,000.

Mercury in Teething-powders

Mr. J. HYND asked the Minister of Health whether he was ware of the widespread sale of children's teething-powders ontaining mercury although no reference to the mercury ontent appeared in the printed analysis; and whether he ould ensure that a full description of such contents was ade a condition of sale in future.—Miss HORNSBY-SMITH eplied: If the hon. member will give me particulars of the ases he has in mind I will bring them to the attention of the harmaceutical Society, who have the duty of enforcing the ppropriate section of the Pharmacy and Medicines Act, 1941.

Mr. HYND asked whether the Minister would make inquiries nto the effects on children's health arising from the wide-pread use of teething-powders containing mercury, and give uch publicity as might be necessary in the interests of parents nd children to the result of his inquiries.—Miss HORNSBY-SMITH replied: Inquiries are already in progress at various hildren's hospitals. Although indiscriminate use of teething-owders is clearly undesirable, there is not yet definite evidence o justify general publicity.

Aged Persons in Mental Hospitals

Mrs. JEAN MANN asked the Secretary of State for Scotland if e would give the total number of patients within mental nstitutions and homes in Scotland and the proportion of these over sixty-five years of age.—Mr. STUART replied: The total number of patients in mental hospitals in Scotland at Jan. 1, 1952, was 20,049. The only available statistics of age-distribution relate to the age of certified patients on admission. During the first four months of 1949 and 1950, respectively, out of 869 and 893 such admissions, 320 and 326 were patients over sixty years of age.

Public Health

Employment of the Tuberculous

THE Ministry of Health, in a circular (7/52), invites local health authorities to coöperate fully with the Ministry of Labour and National Service in the occupational resettlement of the tuberculous. The Minister of Health, says the circular, is advised by his Standing Tuberculosis Advisory Committee that there need be no general bar against placing in ordinary employment people with open tuberculosis, provided that the placing of the individual in the particular employment concerned is subject to medical guidance and approval. The circular continues:

> "There is experience to show that no harm has come of admitting such persons to ordinary employment so long as the work undertaken is in medical opinion suited to the individual's physical capacities and unlikely to prejudice his own health or involve risk to the health of others, and so long as he can be relied on to exercise that personal care which tuberculosis patients are trained to take. It is obviously desirable that the employment of infective tuberculous persons should be medically controlled in this way through arrangements under the Disabled Persons (Employment) Act, rather than that they should be excluded from these arrangements and left to find work for themselves, possibly in unsuitable employment and without disclosing that they are tuberculous."

Disablement resettlement officers are accordingly not to be precluded from trying to find employment for a person with open tuberculosis in work suited to his capacities, as assessed by the chest physician and reported by him to the D.R.O. Such a person will, however, not be placed in a job which the D.R.O. feels may be suitable until this placing has been medically approved. This approval will call for association between the medical officer of health and the chest physician; and it will be desirable for the patient's own doctor to be consulted.

Variola Minor in England

In the week ended April 12 notifications of variola minor in south-east Lancashire numbered 1 at Rochdale and 2 at Littleborough; there is now some doubt as to the diagnosis in a 4th case notified from Wardle. Contacts remain under surveillance at Rochdale, Littleborough, and Chadderton. No further case has occurred in Aldershot, and contacts are now out of surveillance.

Register of the Blind

During the year ended March 31, 1951, the number of registered blind persons in England and Wales increased by 2144 from 81,320 to 83,464. Registered blind people in employment numbered 9858 (an increase of 223), and those undergoing training 742. Of the 9858 employed blind people 4573 were engaged in special workshops or in their own homes.

Over forty occupations are followed by blind people. Basket-making heads the list (1350), followed by factory work (952), machine knitting (742), and brush-making (660). Other blind people are agricultural workers (123), gardeners (73), clerks and typists (305), office executives (34), school-teachers (39), and ministers of religion (46). Homes especially established for the blind accommodated 2013 (an increase of 213), and the number of blind people in other homes provided by local authorities rose by 235 to 1966. New cases registered during the year totalled 11,155—505 more than in the previous year.

The Athens School of Hygiene

The School of Hygiene at Athens was founded in 1929 under the auspices of the League of Nations and the Rockefeller Foundation. It did well for a time, but the war came and ten years of continuous political struggle practically wrecked the school, which lost much of its equipment and personnel and fell so low that it almost passed out of existence. The political situation having improved, the government, with the help of the World Health Organisation and the Rockefeller Foundation, determined to reorganise the school, and it invited Brigadier G. S. Parkinson to draw up a plan for reconstruction.

The choice was a wise one; for Brigadier Parkinson, as a former dean of the London School of Hygiene and Tropical Medicine, has great experience in the field he was asked to survey. Having accepted the task he pursued it with enthusiasm, and after spending much time in making himself familiar with local conditions, he reported his proposals. Naturally, he chose the London school as his model; but modification was necessary to suit local conditions, including Greek finance, culture, and the legal system. He succeeded so well that it seems likely that the Greek government will implement his proposals without material alteration. Only the minimum changes necessary to put the school on a sound footing are possible. These are, nevertheless, fairly drastic. The first necessity is a new charter to give the school independence.

Progress in Uganda

Between 1921 and 1931 the African population of Uganda increased by 500,000, and it is estimated to be increasing now at the rate of 1·9% per annum. The population in 1950 was computed to be 4,846,000. This gives some idea of the problems facing the medical administration, which has been handicapped by a shortage of staff, though this is being overcome.

The principal causes of disease and disability are malaria, venereal disease, yaws, ophthalmic conditions, respiratory infections, rheumatic conditions, skin conditions, and violence; and these, together with tuberculosis, disorders of pregnancy and the puerperium, and intestinal obstruction, account for a large number of deaths in hospital. In the background, of course, lies malnutrition, particularly protein deficiency. The report of the medical department for 1950 notes advances against tuberculosis, 50 of the 653 beds at Mulago Hospital being handed over for treatment of this disease; against leprosy, in which the new sulphone drugs and thiosemicarbazone are being used; and in maternity and child-welfare services, resulting in an increase in the proportion of live births in institutions to a level 13% above that in 1949. Attention has been devoted to the health education of the African, with encouraging results. The training-school for Africans at Makerere College is increasing in efficiency; the clinical teaching is now in the hands of a full-time staff, and the curriculum has been lengthened from six years to seven.

Appointments

Arkle, D. J., B.M. Oxfd, M.R.C.P., D.P.M.: consultant psychiatrist, general and mental hospitals of the Reading area, and deputy physician-superintendent, Fair Mile (Mental) Hospital, Berkshire.

Armstrong, C. A. G., M.B. Belf., D.A.: anæsthetist, Mid-Ulster Hospital, Magherafelt, and the South Tyrone Hospital, Dungannon.

Cheshire, P. S., M.R.C.S., D.A.: part-time consultant anæsthetist, County Hospital, Lincoln.

Edwards, Harold, C.B.E., M.S. Lond., F.R.C.S.: surgeon, Italian Hospital, London.

Ferguson, Catherine, M.B. Dubl.: asst. county M.O.H., Warwickshire County Council.

Gray, Harry, M.D. Leeds, D.P.H.: M.O.H., Flaxton and Easingwold Rural District Councils and asst. county M.O., North Riding of Yorkshire.

Lubicz-Sawicka, Alicia, M.B., Polish School of Medicine, Edin.: asst. M.O. for maternity and child welfare, Sheffield.

McNeil, N. L., M.B. Lond., D.O.M.S.: asst. ophthalmologist, Barnsley area.

Moore, H. C., M.D. Lond.: director of pathology, bacteriology and biochemistry, Rotunda Hospital, Dublin.

Scott, B. O., M.R.C.S.: asst. to physician i/c of physical medicine, United Oxford Hospitals.

Szarnagiel, Zophia, M.B. Polish School of Medicine, Edin.: asst. M.O. for maternity and child welfare, Sheffield.

The Terms and Conditions of Service of Hospital Medical and Dental Staff apply to all N.H.S. hospital posts we advertise, unless otherwise stated. Canvassing disqualifies, but candidates may normally visit the hospital by appointment.

Diary of the Week

APRIL 20 TO 26

Monday, 21st

Royal Eye Hospital, St. George's Circus, S.E.1
5 P.M. Dr. T. H. Whittington: Science and Art of Refraction.

Hunterian Society
7 P.M. (Talbot Restaurant, London Wall, E.C.2.) Mr. C. Robert Rudolf: Hunteriana—part II.

Tuesday, 22nd

Royal Eye Hospital
5 P.M. Prof. Arnold Sorsby: Genetics in Ophthalmology.

University of Edinburgh
5 P.M. (University New Buildings, Teviot Place.) Prof. J. C. Eccles, F.R.S.: Plastic Changes in the Reflex Responses of the Mammalian Spinal Cord. (Macarthur lecture.)

Wednesday, 23rd

Royal College of Surgeons, Lincoln's Inn Fields, W.C.2
5 P.M. Mr. Hugh Donovan: Tuberculosis of the Urinary Tract.

Royal Eye Hospital
5.30 P.M. Mr. L. H. Savin: Ophthalmic Injuries.

Royal Institute of Public Health and Hygiene, 28, Portland Place, W.1
3.30 P.M. Dr. Mary D. Sheridan: Avoidance of Injury to Children at Play.

University of Oxford
5 P.M. (Radcliffe Infirmary.) Mr. W. R. Douglas: Clinical Approach to the Problem of Malignant Cervical Glands.

Thursday, 24th

Royal Eye Hospital
5.30 P.M. Miss J. M. Dollar: Postoperative Complications and their Management.

St. George's Hospital Medical School, Hyde Park Corner, S.W.1
5 P.M. Dr. Desmond Curran: Psychiatry lecture-demonstration.

Westminster School of Medicine, Horseferry Road, S.W.1
5.30 P.M. Prof. N. F. Maclagan, Dr. R. D. Tonkin, Mr. A. G. Jessiman, Dr. C. F. Scurr: Electrolyte Therapy in Surgery.

Royal Society of Medicine
8 P.M. *Section of Urology.* Mr. A. I. L. Maitland, Dr. J. H. Wright: Unilateral Renal Hypertension.

Royal Army Medical College, Millbank, S.W.1
5 P.M. Mr. St. J. D. Buxton: Arthroplasty.

West End Hospital for Nervous Diseases
5.30 P.M. (Department of Psychiatry, 48, Cosway Street, N.W.1.) Dr. E. H. Larkin: Demonstration of physical methods of treatment.

Alfred Adler Medical Society
8 P.M. (11, Chandos Street, W.1.) Prof. R. Dreikurs (Chicago), Dr. N. R. Beattie, Dr. J. Bierer: Essentials of Individual Psychology.

Renal Association
4.30 P.M. (41, Portland Place, W.1.) Dr. W. J. Dempster: Nature of the Disintegration of Homo-transplanted Kidneys in Dogs. Dr. H. de Wardener and Dr. B. E. Miles: Auto-regulation of the Renal Circulation.

Manchester Medical Society
8.15 P.M. (University of Manchester.) *Section of Anæsthetics.* Dr. E. S. N. Fenton: Anæsthesia in Cardiac Surgery. Dr. J. R. Esplen: Description of a Simply Constructed Mechanical Respirator (Spiro-pulsator).

University of St. Andrews
5 P.M. (Medical School, Small's Wynd, Dundee.) Professor Eccles: Plastic Changes in the Reflex Responses of the Spinal Cord.

Friday, 25th

Royal Society of Medicine
8 P.M. *Section of Obstetrics and Gynæcology.* Prof. J. C. McClure Browne, Mr. W. Hawksworth: Present Conception of Trial Labour. Dr. Derk Crichton: Accuracy of X-ray Cephalometry in Utero.

Institute of Laryngology and Otology, 330–332, Gray's Inn Road, W.C.1
4.30 P.M. Mr. G. W. Watkyn-Thomas: Hearing-aids.

Medical Society for the Study of Venereal Diseases, 11, Chandos Street, W.1
7.30 P.M. Dr. D. J. Campbell: Recent Experiences and Problems.

British Association of Physical Medicine
11.45 A.M. (Royal Free Hospital, Gray's Inn Road, W.C.1.) Discussion on manipulation.

Empire Rheumatism Council
4.30 P.M. (Arthur Stanley Institute, Peto Place, Marylebone Road, N.W.1) Dr. W. S. C. Copeman: Recent Advances in Rheumatic Diseases.
4.30 P.M. Dr. Oswald Savage: Rheumatoid Arthritis.

Saturday, 26th

British Association of F
11 A.M. (Royal College
2.30 P.M. (Royal Nat Stanmore.)
Poliomyelitis demonstration.

Empire Rheumatism Council
10.15 A.M. Dr. G. R. Fearnley: Gout.
11.30 A.M. Mr. Norman Capener: Orthopædic Aspects of Rheumatic Diseases.
2 P.M. Dr. Doris Baker: Non-articular Rheumatism.
4.15 P.M. Dr. H. F. West: Ankylosing Spondylitis.

Notes and News

UNMARRIED MOTHERS

THERE was a time when the illegitimate child had—almost definition—no legal rights; but fortunately views have anged. Indeed he now has such complicated rights that the ational Council for the Unmarried Mother and her Child[1] ve appointed a legal subcommittee to study the laws lating to him and his mother, both in the Dominions and sewhere abroad, and to consider whether new legislation is eded here. The chairman of the committee is Mr. Warden owing, and Dr. Letitia Fairfield and Dr. Albertine Winner e among the members.

Subjects suggested for study include the position of social orkers asked to give evidence about information acquired nfidentially, and the questions whether the courts should ear affiliation cases in private, whether the fixed maximum m should be abolished in favour of a sum depending on the atus of both parents, whether the order should be given gainst more than one putative father, and whether enforce-ent officers are useful. The committee will also reconsider e difficult problem of inheritance, and the question of ostmarital legitimisation—which at present is only possible hen both parties were free to marry at the time of the ild's birth.

At the request of the Home Office the council is trying to oördinate the work of many agencies designed to help reign-born mothers and their illegitimate children born in is country. In many cases, of course, these children have ritish fathers; their mothers are in a particularly hard osition, for religion, language, customs, and even food are nfamiliar to them. Another difficult problem is provided y the illegitimate children born to German women by British roops stationed in Germany. Neither the War Office nor the oreign Office seem able to help, and the council can do little; hey do, however, act as a forwarding agency, thanks to a oncession by the Board of Trade, to send money given under oluntary agreements by British men to their German hildren. A similar problem arises where United States orces are stationed in this country, but the American uthorities are more helpful, and often ready to accept esponsibility.

The council has also given advice on legal matters, on the ostering of young children, and on the education of older hildren, made arrangements for confinement, traced putative athers, found suitable work for mothers who wish to keep heir children with them, and administered training grants rovided by the Lord Mayor's Fund.

A HOME IN SOUTH LONDON

The report gives no details about homes and hostels for unmarried mothers, though the council have a committee to encourage the work of such homes. Many good homes now exist, fortunately. A rather specialised home of the kind, lately described to us, receives educated girls who would not fit easily into the usual type of home. Run by the Fellowship of St. Michael and All Angels, it is situated in a comfortable Victorian house in South London, with a large garden, a big nursery, and good sitting-rooms. Before they are delivered the mothers sleep two to a room, but afterwards each has an airy well-furnished bedroom for herself and her baby. Every baby spends most of the day in a perambulator in the garden. The births take place in a neighbouring hospital where the mothers are admitted for ten days.

The matron, doubly qualified in nursing and midwifery, has qualities of character and spirit which enable her to help these young people in difficulties. The home expresses its religious background in many ways. There are daily prayers in a small beautiful chapel, at which attendance is voluntary, though most like to come. Besides the matron there is another sister, a resident cook, and a daily help. The housework is shared by the residents. Unfortunately only about one in ten of the mothers are able to keep their babies with them, but none of them leaves the home until her future is assured. A part-time secretary gives them much help in planning what to do. They stay six weeks after delivery, and feed their babies for a month, the last fortnight being taken for weaning.

The residents pay £3 3*s.* a week, some being helped with fees by their county authorities; but in the main the home, which is affiliated to the Church of England Moral Welfare Council, depends on voluntary contributions.

CHEMOTHERAPY AND THE ANTIBIOTIC DRUGS

UNDER this title the Fellowship of Postgraduate Medicine have republished in booklet form nine articles from the *Postgraduate Medical Journal*. Dr. C. A. Keele has added an article on the principles of chemotherapy to introduce the anthology. There follow accounts of the chemotherapy of pulmonary tuberculosis, non-tuberculous diseases of the chest, tuberculosis elsewhere than the lung, venereal diseases, tropical infections of the bowel, malaria, and infections of the urinary tract. The collection has brought together much up-to-date information not otherwise obtainable in so compact a form. The price is 5*s.*, and the address of the fellowship is 60, Portland Place, London, W.1.

DOCTOR IN THE HOUSE

Richard Gordon's story of student life at St. Swithin's Hospital[1] bears on its title page the scathing judgment of medical students given by Bob Sawyer's landlady. But this particular "parcel of lazy, idle fellars" gets through in the end—and only one cheated. The humour of it is indeed Pickwickian in parts; there is a figure reminiscent of Mr. Jingle who contrives to fail his examinations because the allowance bequeathed by his grandmother stops when he qualifies. Boisterous fun is unlimited. The "jape" on the Dean would have earned top marks in the fifth form at Greyfriars, and the senior surgeon at St. Swithin's is drawn so devastatingly that his colleague in *The Doctor's Dilemma* seems a paragon by his side. The examination scenes contain some of the funniest disasters that never befell a student, and we even meet those legendary examiners who, having asked a question, spend the rest of the viva arguing about the right answer. The author assures us that St. Swithin's, its staff, patients, and students do not exist, but his medical readers will surely recall in their own hospitals the counterparts of some of his less outrageous characters.

NEW FILMS ON ANTI-HISTAMINE DRUGS AND ON SIALOGRAPHY

THE documentary film unit of Messrs. May & Baker Ltd. have made two new sound films in 16 mm. colour and offer to show them to medical or nursing groups at home or overseas. The longer one (32 minutes), on *Anti-histamine Agents*, was made with the help of the pharmacological departments of Leeds and Edinburgh Universities. Starting with the experimental work of Dale and Laidlaw, who first demonstrated histamine in ergot of rye, it shows how injections of this substance into guineapigs simulates the weal and flare of urticaria, or, in bigger doses, causes the rapidly fatal bronchospasm characteristic of "anaphylaxis." The scene then moves to France, where Fourneau, one of the few great men who has appreciated a pun on his own name, joined in the search for antagonists to histamine. After working systematically through hundreds of synthetic compounds, in 1942 he at last discovered the first potent anti-histamine drug with a toxicity low enough to be tried clinically. This compound is still widely used on the Continent and in the U.S.A. The film next illustrates the protection given by the newer anti-histamine compounds to guineapigs against fatal anaphylaxis and to man against an intradermal injection of histamine. After this we are shown two of the most delightful shots in the film—timothy-grass rippling in a summer breeze, and a skilled ploughman with his pair of horses in action on stubble. On the whole, the film covers the impracticably big subject with commendable clarity, though some parts might well be discarded so that others can be taken at more leisurely speed. The second film, *Sialography Technique*, running for 15 minutes, presents a much more straightforward subject for both the audience and the makers. The photography, especially the brilliant colour photographs of the openings of the salivary ducts inside the mouth, is admirable. Perhaps too much film is given up to trays laid out for the surgeon, and we could have done with a few more hints on common difficulties and how to overcome them. Otherwise the practical details—of the simply made catheters for introducing the opaque medium; the posturing of the patient on the X-ray table, and so on—are well covered. The elocution of the main speaker deserves special commendation. There is a filmstrip showing typical sialograms, intended for surgeons, radiologists, and radiographers and for teachers.

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[1] Thirty-first Report, May, 1950–April, 1951. Obtainable from the Secretary of the Council, 21, Coram Street, London, W.C.1. Pp. 44.

[1] Doctor in the House. By RICHARD GORDON. London: Michael Joseph. 1952. Pp. 190. 10*s.* 6*d.*

PUBLICITY FOR DRUG-ADDICTION

INFORMATION about drug-addiction was given to the public in two ways last week—in an illustrated magazine and in a television programme.

Discussing the possible dangers of such publicity, a writer in *Picture Post*[1] says that "the Home Office and Scotland Yard take the view that publicity might arouse morbid excitement among the unstable or curious." But the problem, he thinks, is too serious to be "left in the air," and the article publishes the findings of an inquiry into addiction in this country. The conclusion reached is that, while addiction is not so grave a matter as in some other countries, there are signs that "it is not as static and local as the official attitude implies." But no evidence of organised distribution of drugs on a large scale was found by the *Picture Post* investigators. Fears about extensive trafficking seem unfounded.

In the B.B.C. television service on April 7 viewers saw an imaginary reconstruction of what might have happened to a young woman in the grip of drugs. She was fortunate enough to be taken to hospital with a broken leg and her illness was discovered. Sympathetic treatment helped her towards recovery, but not without harrowing pangs of abstinence. Explanatory passages by doctors in the hospital were ingeniously fitted into the story. When the man who had supplied the drugs to the girl was discovered, it was surprising to learn that he had been getting quite large quantities for the past year on a doctor's prescription given for a form of neuralgia. The programme was clearly and entertainingly presented. Propaganda put over as well as this need raise no fears of encouraging experiments with drugs.

University of Oxford

Sir Russell Brain, P.R.C.P., has been elected to an honorary fellowship at New College, of which he was a commoner from 1914 to 1919.

University of London

Mr. F. Bergel, D.SC., F.R.I.C., has been appointed to the chair of chemistry at the Institute of Cancer Research.

University of Edinburgh

Dr. Douglas Guthrie will give six lecture-demonstrations on the history of medicine at 5 P.M. on Mondays and Thursdays from May 22 to June 9.

National University of Ireland

Dr. Oliver FitzGerald has been appointed lecturer in therapeutics.

Society of Chiropodists

This society's annual convention is to be held in Manchester on April 24–26.

Newsholme Lectures

Sir Edward Mellanby, F.R.S., will deliver these lectures at the London School of Hygiene and Tropical Medicine, Keppel Street, W.C.1, at 6 P.M. on Wednesday, Thursday, and Friday, May 14, 15, 16. He will speak on Medical Research—its Methods, Problems, and Social Significance.

International Congress of Radiology

The seventh International Congress of Radiology is to be held in Copenhagen from July 19 to 25, 1953. Further particulars are to be had from the congress office, Øster Voldgade 10, Copenhagen K, Denmark.

Maternity "Wing" for Charing Cross Hospital

Kingsbury Maternity Hospital, Honeypot Lane, London, N.W.9, has been made a member of Charing Cross Teaching Hospital Group.

National Old People's Welfare Committee

In October the committee is starting a four-month training course for women between the ages of 27 and 50 who wish to become wardens of old people's homes. Six weeks' theoretical training will be given at a centre in London, four weeks' practical training in the geriatric units of London hospitals, and six weeks' practical training in statutory and voluntary homes. Further particulars may be had from the secretary of the committee, 26, Bedford Square, London, W.C.1.

British Association

This year the association will meet in Belfast from Sept. 3 to 10, under the presidency of Prof. A. V. Hill, C.H., F.R.S.

Institute of Orthopædics, London

The sum of £1000 has been given to the institute for the support of research in poliomyelitis. The donors, who wish to remain anonymous, lost a young friend some months ago from a rapidly fatal attack of the disease.

Glasgow Medical Exhibition

On Monday, May 26, at 11.30 A.M., Dr. W. W. Galbraith will open the exhibition at St. Andrew's Hall, Glasgow. The exhibition is organised by the British & Colonial Druggist Ltd., who are also organisers of the London Medical Exhibition.

Overseas Science Students' Association

At a meeting held on March 19, this association was instituted. Its aims are to bring graduate science students from overseas into contact with the scientific life of Great Britain and with one another. Further information may be had from Mr. P. Sen, the secretary, c/o Society for Visiting Scientists, 5, Old Burlington Street, London, W.1.

Ophthalmic Nursing Board

This board has been established to promote and maintain a general standard of efficiency in ophthalmic nursing. A syllabus of training has now been issued, and examinations will be held for a diploma in ophthalmic nursing. The board is empowered by its constitution to decide which hospitals shall be recognised as providing the required course of instruction for the diploma. The board may be addressed at Moorfields, Westminster, and Central Eye Hospital, City Road, London, E.C.1.

EMERGENCY BED SERVICE.—In the week ended last Monday (April 14) applications for general acute cases numbered 961. The proportion admitted was 91·9%.

CORRIGENDUM: *Paroxysmal Auricular Fibrillation.*—In the autobiographical article on p. 761 of our last issue the date of the patient's first attack should have been stated as 1926, not 1936.

A *Directory of Contributory Schemes* for 1952 has been published, and copies may be had from the British Hospitals Contributory Schemes Association (1948), Royal London House, Queen Charlotte Street, Bristol, 1 (price 10*s*.).

The Queen of the Netherlands has conferred on Dr. H. M. Sinclair the insignia of an officer in the Order of Orange Nassau in recognition of his services during the late war while director of the Oxford Nutrition Survey.

On June 1 Dr. Stanley E. Bradley will succeed Dr. Eugene B. Ferris as editor-in-chief of the *Journal of Clinical Investigation*; and the journal's offices will be transferred to Presbyterian Hospital, 620, West 168th Street, New York 32, N.Y.

Births, Marriages, and Deaths

BIRTHS

COLES.—On April 7, in Northampton, the wife of Dr. R. B. Coles—a daughter.

DUNN.—On April 9, the wife of Dr. T. B. Dunn, of Woodford Green, Essex—a daughter.

FLEWETT.—On April 1, in Leeds, the wife of Dr. T. H. Flewett—a daughter.

HAGGER.—On April 3, the wife of Dr. A. O. Hagger—a daughter.

HALL.—In Dover, the wife of Dr. D. W. Hall—a daughter.

MACARTHUR.—On April 5, in London, Dr. Hilary Macarthur (née Parton), the wife of Mr. Angus Macarthur, F.R.C.S.—a son.

RICHARDSON.—On March 29, the wife of Dr. A. T. Richardson, of Surbiton—a son.

SANGER.—On April 8, in London, the wife of Dr. Cyril Sanger—a son.

MARRIAGES

NEWMAN—KENNING.—In London, Charles Newman, F.R.C.P., to Mrs. Phyllis Kenning.

DEATHS

FLEMING.—On April 3, at Surbiton, Robert Hood Fleming, M.B., B.SC. Lond., F.R.C.S., aged 62.

HOSFORD.—On April 10, John Stroud Hosford, F.R.C.S.E., of London and Bexhill-on-Sea.

LESLIE.—On April 7, Leonard Leslie, M.D. Edin., of Streatley, Berks.

RONALDSON.—On April 5, James Bruce Ronaldson, O.B.E., M.A., M.D. Camb., of Little Chalfont, Bucks.

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[1] *Picture Post*, April 12, 1952, p. 22.

AFTER FIFTY-SIX YEARS *

SIR JAMES LEARMONTH
K.C.V.O., C.B.E., Ch.M., LL.D. Glasg., F.R.C.S.E.,
Hon. F.R.C.S.
EGIUS PROFESSOR OF CLINICAL SURGERY AND PROFESSOR
OF SURGERY, UNIVERSITY OF EDINBURGH

PERHAPS the most hallowed place where a surgeon may ause to meditate for a moment is before the arch behind he lecture-theatre in the Sorbonne, upon which it is ecorded so simply and yet so utterly adequately, " Here great Englishman was embraced by a great Frenchman." his meeting between Lister and Pasteur was symbolic f the interdependence of surgery and sciences other than urgery, an interdependence so near Lister's heart that is presidential address to the British Association in 896 was devoted to it. It seemed to me not unfitting hat fifty-six years later I might include in my oration ome consideration of the influence of Lister's familiarity ith other scientific disciplines upon his life and upon is work; that I might recall Lister's accounting of the ontributions made to surgery by other sciences; and hat I might record, with their implications for the uture, some of the contributions to surgery made by hese sciences since Lister's time.

In any such accounting, whether in Lister's time or ow, the number of operative contributions falls short of he potential number. The reasons for this deficit are ell known. The majority of contributions have their rigin in the discovery of some new fact or process in a aboratory. It may take some time for such a discovery o be accepted in its own discipline, a delay which rotter attributed to " an ingrained quality of the mind," nd therefore often an inevitable delay. In any branch f science which may have practical applications there is possibility of further delay between the acceptance of he discovery and its incorporation into the practice of ts own science, or into the practice of related sciences. In edicine this latter delay is often more apparent than eal, because very properly time has been spent in making controlled experimental and clinical trials of the possible applications of the discovery.

Lister's own innovation was derived from the laboratory. Its general adoption was retarded by delays of both categories, which provided almost the only vexation that disturbed the serenity of his long life. But although the difficulties which beset his innovation tried Lister's patience, they did not obscure in his mind the two tasks of any innovator. These were so clear to him that they ordered his whole professional life. His first task was to convince men of his own era who held other views; at the outset the verdicts of his colleagues upon his work were seldom equitable. " A froward retention of custom," wrote Bacon, " is as turbulent a thing as an innovation." Lister's second task was to train his pupils in the right way from the first. In this connection it must be remembered that Listerism was a break of considerable violence in the continuity of the practice of surgery. Although nowadays it may seem to us to have been a relatively simple exercise, in the '70s of last century compliance with Lister's technique imposed upon both teacher and taught a series of rigid " dos " and " don'ts " unfamiliar in operating-theatre and ward. To offset these irksome difficulties Lister had one conspicuous advantage. His was a great crusade. Unlike many crusades, which winnow out from the ranks of their supporters men and women of sufficient calibre to direct them, the crusade against wound infection had from its very beginning a leader worthy of it, a leader whose high intellectual stature stamped the crusade as of first importance.

One subsequent difficulty may be noted. Delay in working advances in medicine into the fabric of human experience, and especially the delay which retarded Lister's innovation, has produced in the minds of a minority of laymen an illogicality which, I imagine, most of us have met. Because formerly (and sometimes quite long ago) certain therapeutic procedures were at first not accepted by our profession, but later came into general use, this minority continues to believe that the only barrier to the immediate acceptance and useful application of every suggested procedure is the blind conservatism of physicians and surgeons, however bizarre the procedure, however unproven the claims made for its efficacy. That such an illogical idea can be seriously entertained is a sad commentary on the habits of thought of this small but often enough vociferous minority.

Lister's Career

Let me now turn to my first topic—the effect upon Lister's work of his familiarity with other sciences. Looked at with the eyes of 1952, the design of Lister's professional life is clear. As has been pointed out by Sir Robert Muir (1933), a previous Lister Orator to whose teaching and inspiration I owe much, Lister's work falls naturally into periods, each of which must be considered in perspective, and also partly in some detail.

1852–1860

(UNIVERSITY COLLEGE HOSPITAL AND EDINBURGH)

The first period—from just a century ago to 1860—was devoted to the study of fundamental physiological and pathological problems by the available laboratory methods. Lister ranged widely, but without over-dispersing his efforts. To this period belong his researches on inflammation, on the pigmentary system of the frog, on coagulation of blood, and on the nervous control of blood-vessels. The results of these investigations were published in a series of important papers.

It does not matter that not all the conclusions which Lister recorded in these papers were correct, although there are critics—to be sure second-rate—who think that such mistakes are serious. The essential quality in an investigator is the ability to think of something to investigate, provided that his observations are made as accurately as is possible at the time. As F. C. Bartlett has recently emphasised, the process by which his observations are pieced together and elaborated provides a better basis for estimating the intellectual power of an investigator than do any conclusions he may reach, however new or even revolutionary they may be. The correct outlook of the wise critic has been concisely stated by G. M. Young: " Errors are opinion in the making."

From the first—and Lister was only 33 years old at the end of this period devoted solely to fundamental research—from the first his method never deviated from the most important tactic in the experimental approach: to set clear and limited problems. From the first, he followed the Aristotelian method of asking himself questions which could be so answered by the experiments he designed as to provide the data required for the solution of these problems. From the first, he pieced together and elaborated these data with the greatest insight and clarity. From the first, therefore, he reached his full scientific stature. As examples of Lister's pursuit of this tactic, let me describe briefly two of his investigations. The conclusions of his important paper on the parts of the nervous system which regulate the *contractions of arteries* embody the results of a piece of pure physiological research which did not find immediate clinical application :

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* The Lister Oration delivered at the Royal College of Surgeons of England on April 4, 1952. The lecture will also appear in the *Annals* of the college.

> "(1) That, of the nervous centres usually recognised, the cerebrospinal axis is the only part which regulates the contractions of the arteries of the webs : this function being apparently exercised by the whole length of the cord and the posterior part of the brain, operating through fibres which arise from the same region of the cord as do those through which sensation and motion are effected in the hind legs."

We know now that vasoconstrictor fibres have a limited origin from the spinal cord, and do not arise from its whole length. We owe this refinement of knowledge to the work of British physiologists on animals, and to accurate and controlled observations made by a large number of surgeons during and after division of sympathetic nerves or spinal roots in man.

> "(2) That there exists within the limb some means, probably ganglionic, by virtue of which the fibre-cells of the circular coat of the arteries may contract in concert with each other, independent of any ganglia contained in the trunk."

This conclusion remains substantially true, although we know now that the mechanism is not ganglionic, but a fundamental property of the smooth muscle in the middle coat of arteries. In the treatment of injuries the existence of this mechanism has sadly plagued surgeons by obtruding itself as arterial spasm. This is unaffected by freeing the contracted artery from the control of its extrinsic nerves ; only recently it has been shown by J. B. Kinmonth to be abolished in certain animals by the local application of a solution of papaverine. If this be true in man also, the method cannot be too quickly incorporated in the surgery of trauma.

> "(3) That the local coördinating apparatus, though capable of independent action in special conditions of direct irritation, is, under ordinary circumstances, in strict subordination to the spinal system : while a remarkable provision exists for the maintenance of this control, notwithstanding almost complete severance of nervous connection between the cord and the limb."

When it is remembered that Lister was writing before adrenaline was discovered. this statement also was broadly true. It provides the hypothesis upon which are based operations for the division of sympathetic vasoconstrictor nerves as part of the management of certain diseases of arteries, and it also provides an explanation for the clinical observation that the vasodilatation immediately following these operations is somewhat reduced by the passage of time.

On the other hand, in his first work on the *coagulation of blood* Lister deliberately chose the experimental laboratory in which to seek an explanation for a clinical phenomenon : he shared the view of his contemporary Huxley, that "experiment is artificial observation." He had amputated a child's leg for gangrene complicating scarlet fever, and within the normal popliteal artery he found a thrombus. In a series of ingenious experiments upon animals, he showed that blood remained fluid in a segment of vein as long as the endothelium was intact, but coagulated after transfixion of the vein by a needle—a procedure which injured the endothelium and introduced a foreign body into the blood. Perhaps not a complete explanation of the process of coagulation : but how much nearer the truth than any previous hypothesis.

There is no doubt that any errors in these beautifully designed and executed pieces of research were but "opinion in the making." As did Lister then, we must work today with the knowledge and with the tools to hand, and it is idle to demand finality in the results of such investigations. Whether or not we now accept Lister's conclusions, we retain undiminished respect and admiration for his genius, his industry and his steadfastness of purpose. There is another important aspect of Lister's work during this first period whic must command our attention. Skilled as he was in th tactics of research, he added to his intellectual statur by limiting his strategic aims. It cannot be too ofte repeated that in his choice of problems a grand desig is clear : he wished to become familiar with every aspec of the response of tissues to injury. No other knowledg could have been more essential to fit him to perfec his subsequent clinical work for practical use.

1860–1869

UNIVERSITY OF GLASGOW

In these days when there is much talk, and often loos talk, about the advantages and disadvantages o specialisation, it is of interest to try to determine how Lister ordered his clinical and operative commitment First, from the evidence of those who were associate with him during his active career there is no doubt that he would have agreed that every would-be surgeon must be reasonably adept in carrying out those practical manœuvres which are common to all surgical operations. Secondly, he knew that the basis of broad operative experience depends upon familiarity with the steps of a sufficient number of standard procedures ; in Lister's early career these were not numerous. Thirdly, as a scientist he must have been keenly aware that conclusion *drawn from a number of cases in which a given procedu* has been used are valid only if each procedure has been performed with the highest possible technical skill.

The evidence is that Lister completed this practical experience during the early years of his tenure of the chair of surgery in the University of Glasgow which formed the second period of his life's work. Soon after he introduced his antiseptic methods in the later part of this period, Lister must have realised that for the *first time* a vast number of desirable new surgical procedures could be safely performed. He resisted the temptation to make this use of his work, although he must have been aware of the great wealth that it would have assured him. Instead he confined himself largely to the surgery of injury and to certain aspects of what we would now call orthopædic surgery, because such cases provided him with the most suitable conditions for refining his methods. For the rest of his life, so far as I can find out, Lister followed the same plan—and how wise that was. He knew that the brake upon the production of original work is not routine, that excuse of the unproductive, but too much routine. He knew that, in the science of surgery, to try to be original all the time is to neglect the wider and equally important duties of translating original work to practice, of shortening the time needed for this and of narrowing the gap between the laboratory and the ward. "It is the second-raters," wrote C. E. Montague, "who pursue novelty at all costs."

1869–1877

(UNIVERSITY OF EDINBURGH)

Certainly Lister continued to restrict the scope of his clinical work when he returned to Edinburgh and entered upon the third period of his career. This was devoted to the refining and simplification of his methods and to the beginning of his campaign to disseminate them throughout the world of surgery. During these years his contributions to surgical literature reflected this purpose. They contained careful statements of his views and of his clinical practice ; patient explanations of errors made by some who imagined, often sincerely enough, that they were following his directions ; and announcements of changes in his methods. Over and over again the pattern was repeated. A good physiologist, he had already realised the effectiveness of summation of stimuli.

In order to acquaint you with the scope of Lister's clinical work in the eight years during which he was Regius professor of clinical surgery, I have made an analysis of the patients admitted to his care. The records were not always complete, but usually it was possible to identify diagnoses.

When Lister took over wards in the Royal Infirmary of Edinburgh the official number of beds in them was 54—Syme had had 70—but as often as not there were up to 16 extra beds and there might also be mattresses upon the floors. In the eight years there were 2283 admissions, which I have classified in a quite arbitrary way:

A. *Emergencies*

1. Wounds and bruises	200
2. Simple fractures and dislocations	239
3. Compound fractures and dislocations	61
4. Head injuries	68
5. Infections of soft tissues	139
6. Burns	44
	751 = 32·9%

It does not appear that Lister selected these cases, but they provided him with abundant material for perfecting his methods of dressing wounds. His operative technique was already so secure that when it seemed to him necessary he exposed *ununited fractures* and treated them successfully by suture or by pegging with bone; perhaps these were devices which he could have pursued more exhaustively, to the immediate benefit of a larger number of selected patients. Of the 61 *compound fractures and dislocations*, amputation was required in 14; the records were not detailed enough to enable me to determine in each case the indication for amputation, but certainly primary destruction of tissue was a much more common indication than superadded infection.

B. *Cases either attracted to or selected by Lister*

1. Tuberculous osteo-arthritis	381
2. Pyogenic osteo-arthritis	160
3. Varicose ulcers	105
4. Deformities	60
5. Tumours of the breast	110
6. Tumours of bone	53
7. Tumours of the tongue, cheeks, and lips	70
	939 = 41·1%

The first three types of lesion seem to have been deliberately chosen by Lister in order that he might test methods of dressing wounds, both to prevent secondary infection (*tuberculous osteo-arthritis with abscess formation*) and to eradicate existing infection (*pyogenic osteo-arthritis* and *varicose ulcers*). As early as 1872 he employed carbolic acid as a sclerosing agent for *varicose veins*, another fruitful field in which he merely pointed the way. *Deformities* (for which he practised osteotomies and tenotomies) and *tumours of the breast* gave him numerous opportunities for entering the tissues by his antiseptic operative technique, and for making extensive dissections. His interest in *tumours of bone* and in *tumours of mouth and tongue* he had as a legacy from his predecessor Syme, "whose teaching," he said in his gentle way, "I do but reflect."

C. *The "General Run" of the surgery of the times*

1. Anorectal conditions (piles, fistulæ)	96
2. Genito-urinary conditions (hydrocele, stricture, calculus, tuberculosis)	154
	250 = 10·9%

To deal with *strictures of the urethra* he invented the set of bougies which goes by his name and superintended its forging; and he practised suprapubic lithotomy for *stone in the bladder*.

D. *Miscellaneous conditions* 258 = 11·3%

The most striking feature of this group was the diversity of the conditions. It included a surprisingly large number of *tumours of the parotid gland*, although I have been unable to trace any other evidence that Lister had a special interest in this difficult anatomical problem.

E. *Curiously infrequent types of case*

1. Abdominal conditions	11
2. Hernias	20
3. Tuberculous adenitis	17
4. Primary amputations	14
5. Goitre	10
6. Aneurysms	7
7. Senile gangrene	6
	85 = 3·8%

It seems clear that Lister did not deliberately seek to deal with *abdominal conditions*, and it is known that he passed on to another surgeon many which came his way. The following 11 cases appeared in his ward journals: ruptured gastric ulcer, "peritonitis," "pantyphlitis," abdominal tuberculosis, ovarian cyst (2), carcinoma of stomach, carcinoma of colon, carcinoma of rectum (2) and "carcinoma of mesentery." F. M. Caird, who attended his wards from 1874 to 1877, recorded that Lister did not care to open the peritoneal cavity, for two reasons, the chilling action of carbolic lotion and its possible irritating effect; and that he passed on abdominal cases to Dr. Thomas Keith, whose results he much admired. Caird also stated that Lister operated boldly on *hernia*, performing radical cures and resecting bowel; yet at a time when hernia and strangulated hernia were common conditions, in eight years only 20 cases of hernia appeared in his journals—12 femoral of which 3 were strangulated, 7 inguinal of which 2 were strangulated, and 1 umbilical. At this time also *tuberculous adenitis of the neck* was common and it seems strange that so few cases were admitted to his care of a type whose complications would have responded to Listerian dressing. The *primary amputations* were for the end-results of injuries, and 6 of the 14 operations involved one or more fingers. *Goitre* has been placed in this group to enable me to record that Lister "scooped out" a bronchocele in 1872 and excised a "nodule" in 1875; he maintained his interest in goitre, and relieved dyspnoea by scooping out masses of carcinomatous tissue; but from correspondence in the possession of the Royal College of Surgeons of Edinburgh it is clear that he was as interested in maintaining the cleanliness of the subsequent fungating wounds.

It is more than strange that Lister's experimental and clinical interest in the problem of ligation of large arteries was not pursued more actively in his wards at a time when *aneurysm* was relatively common. The 7 cases of vascular disease included 5 popliteal aneurysms, 1 abdominal aneurysm, and 1 varicose aneurysm of unspecified origin. *Senile gangrene* was not so common in Lister's time as it is now that people live longer.

1877–1896

(KING'S COLLEGE, LONDON)

The fourth and final period includes the time Lister spent at King's College. Here his mission was apostolic, and there is little doubt that the move from Edinburgh was undertaken to favour that purpose. He knew that it was for the ultimate good of his crusade to concentrate uninformed criticism and especially ill-natured criticism upon himself, because such criticism too long directed against the same person or against the same proposition steadily loses point.

The story of this period is known to you all: today the only phase that we need to recall is Lister's ultimate triumph, and the distinction which it brought to British surgery. Perhaps as good an indication as any of the enduring success of Lister's crusade is to be found in the tribute of no less a giant than Rutherford Morison, written as recently as 1927:

> "Present fashion in surgery dictates a dry technique and I followed it until two surgical calamities (gas gangrene) pulled me up. Both occurred in clean cases, months apart, in different hospitals. Our sterilising machinery was of proved efficiency, nothing but instruments entered either wound, and both patients died within three days. In thousands of operations performed on antiseptic lines, I had never had such an experience. The calamities occurred in the 300 to 500 cases in which the dry method was practised."

Even fifteen years after Lister's death, his carbolic spray may be said to have obscured Morison's usually clear view.

I have heard it contended—although not in this country—that during his professional life and particularly during this fourth period Lister ought to have turned his highly developed powers of research to more than one major problem, and that if he had done so his genius was such that surgical science would have advanced faster than it did then and subsequently. The contention is plausible enough to require examination. There are at least three possible reasons for Lister's decision. He probably realised that the validity of deductions from the results of surgical procedures does not differ from that of deductions from experiments in the sciences, in that both depend in part upon the elimination of as many variables as possible; only by limiting his problems and his operative work could this condition be observed. We may even hazard that with his mathematical knowledge he recognised the value of a large number of similar experiences in eliminating the influence of chance upon his conclusions. But I think that the major reason for Lister's decision to limit the scope of his work was that he realised the practical advantage of short steps between idea and application, and chose to give himself this advantage by personally shepherding his innovation through all its fascinating stages—the *pure science* of his laboratory, the *investigations* in his wards, the *technology* of application on an ever-increasing scale in his own wards and in the wards of his converts and of his pupils, and the determined *enterprise* to bring his methods to the notice of surgeons all over the world. If this can be called specialism, surely it is the right sort: to distil one's experience, to publish it for the information of one's colleagues, and so, by sharing one's special knowledge, to encourage the disappearance of one's own specialty.

Lister's Scientific Creed

Lister relinquished his chair at King's College in 1893 and gave up private practice in 1896, the year of his presidential address to the British Association. Since this address was given at the end of his professional career, at a time when he was still fresh from the practical problems of surgery, it may be regarded as his scientific creed, and thus it provides the substance of my second topic.

The title of the presidential address was On the Interdependence of Science and the Healing Art. I have found it instructive to consider the import of this address under two headings—its inclusions and its omissions.

THE INCLUSIONS

Almost at once Lister referred to the discovery of röntgen rays, at that time only a year old, and cited examples of its clinical importance, some of which must have been a little beyond the comprehension of even highly intelligent laymen. He described the use of the fluorescent screen, and warned that over-exposure to the rays might be irritating. Moreover he clearly foresaw the extended use which would come to be made of X rays, for he concluded that there was "no reason to suppose that the limits of the capabilities of the rays in this way have yet been reached."

Next Lister noted that the year 1896 was the jubilee of anæsthesia in surgery and reaffirmed his confidence in chloroform: even as a dresser, he had been a little bewildered if it did not act perfectly.

Naturally enough, a large part of the address was a consideration of the steps by which he had arrived at his antispetic system. Lister was always careful to acknowledge his indebtedness to Pasteur. He was able to speak of bacteriology as a science, for Koch's book had been published in 1878. Immunology had made considerable progress, and he described how protection could be provided against rabies and diphtheria. He was alive to the light thrown by the zoologist Metchnikoff on the defensive rôle of leucocytes, the emigration of which had been described by Cohnheim. He permitted himself a filial statement on the place of the microscope in the investigation of the morphology of bacteria: "The improvements of the microscope, based on the principle established by my father in the earlier part of the century, have apparently nearly reached the limits of what is possible." Other forms of microscope—for example the electron microscope—were far in the future.

THE OMISSIONS

It is of some interest that the implications for surgery of the rapidly growing science of organic chemistry seem for Lister to have been concerned only with the choice and preparation of substances for use in dressings. By synthesising urea in 1828, Wohler had laid the foundation of both qualitative and quantitative analyses of organic substances and of the multiplication of these substances in the laboratories of organic chemists and pharmacologists. However Lister's views on the pharmacology of carbolic acid were utilitarian and confined to its physical properties: "The energy of action of any substance upon the human tissues depends not only upon the proportion in which it is contained in the material used as a vehicle for its administration, but also upon the degree of tenacity with which it is held by its solvent." This purely arithmetical view is the stranger, because before Lister left Edinburgh for King's College he must have been aware of the great potentialities inherent in the coöperation of chemist and clinician; his colleagues Crum Brown of the chair of chemistry and Fraser of the chair of materia medica had shown that the addition of a methyl group to certain alkaloids conferred on the new compounds a curare-like action. Yet when a case of tetanus was admitted to his care, the ward journal recorded that Professor Lister ordered—of all drugs—the Calabar bean. Moreover although Claude Bernard had begun to emphasise the importance of the constant composition of the body-fluids as early as 1878, his ideas took even longer to permeate surgical practice than did Lister's; indeed Lister does not seem to have been aware of them.

Contributions Subsequent to Lister's Address

In dealing with my third topic, it will be impossible to make a complete survey of advances in the sciences which have been of direct or indirect assistance to surgeons since Lister's address in 1896; but before making my selection I should like to record one other ever-increasing debt.

This is to the profession of *nursing*, at once an art and a science. The existence of a highly trained and devoted body of women and men is inseparable from and indispensable to the practice of modern surgery; in both ward and operating-theatre it is never easy to draw a dividing line between surgical care and nursing care, nor is it desirable to attempt to do so, for they are one. Moreover a belief that I have now held for more than thirty years has a factual although perhaps not a strictly scientific basis: that when on occasion formal treatments and remedies fail, it is possible for a patient to be nursed back to life and health.

PHYSICS AND CHEMISTRY

Only two years after Lister made his almost dramatic reference to röntgen's discovery, Walter Cannon, while still a medical student, introduced the use of a radio-opaque medium to study the movements of the alimentary tract, a method of physiological investigation soon to be adopted for diagnostic purposes. The principle has since been applied to the study of normal and pathoogical conditions of the urinary tract, the biliary pparatus, the blood-vessels, the subarachnoid space, nd the respiratory tract. Physics has provided us ith devices through which many of the cavities of the ody can be directly inspected; although occasionally ome pessimist warns us against them, it is important o remember that the clinician's own eyes and own hands re still being as effectively used and as effectively rained when he is employing such aids to diagnosis s when they were not available to him. Physics has lready provided for us a variety of instruments for aking and recording biological measurements of great ccuracy; and, most hopefully for the future, physicists re willing to design for us apparatus for investigating lmost any physiological function which we may esignate.

The therapeutic effect of radium and X rays on new rowths has become the separate specialty of radiotherapeutics with its vast complexity of apparatus, the apabilities of which have not yet been assessed. In ecent years the development of atomic physics has ermitted us to trace the distribution and fate of various lements in the living body; some of these elements roduce radiations which favourably influence certain rocesses of disease, and these we can distribute by the lood-stream to the affected parts.

The debt of anæsthetists to chemistry has become nfinitely greater with the advent of the anæsthetic ases, of local and spinal anæsthesia, of intravenous næsthesia, and recently of what Gillies has called "physiological trespass" to provide a bloodless field f operation by the deliberate production of hypoension. This last refinement would have greatly nterested Lister, because he would have recognised in t an extension of his work on the parts of the nervous ystem which regulate the calibre of arteries.

BACTERIOLOGY

As has been so fascinatingly described by a previous Lister Orator, who played a chief part in the near-drama (Florey 1945), bacteriology and organic chemistry have given us those remarkable substances, drugs of the sulphonamide group and antibiotics derived from lowly forms of vegetable life, so potent that within a decade the mortality and morbidity resulting from many infective processes were reduced to an almost unbelievably low incidence. Lister would have rejoiced in modern chemotherapy; but he would *not* have used it to offset any lowering of standards in his techniques. Methods of immunology have made notable progress since 1896; one index may be recorded of their efficiency when employed on a large scale. During the period from "D-day" to "VE-day," fewer deaths from tetanus complicating military wounds occurred in the thoroughly immunised British Liberation Army than occurred from tetanus complicating accidental injuries in the unprotected population of Scotland.

PHYSIOLOGY, BIOCHEMISTRY, AND PHARMACOLOGY

Perhaps our longest list of recent indebtedness is to the linked sciences of physiology, biochemistry, and pharmacology; a burden of debt to some extent offset by the contributions of surgeons to these sciences, partly from observations made possible as a result of the extension of surgical procedures, for example to endocrine glands; and partly as a result of an ever-growing biological approach on the part of surgeons to the pathological problems confronting them. There is the science of endocrinology, beginning with the short announcement of Oliver and Schafer On the Physiological Action of Extract of the Suprarenal Capsules, and still expanding rapidly. There are the anticoagulant drugs, which have overcome difficulties that Lister investigated with anxious solicitude. There is the vast accumulation of knowledge of nutrition from "vitamins" to postoperative nitrogen katabolism; knowledge which has so profoundly and advantageously affected our treatment of injuries and our preoperative and postoperative management of surgical conditions; knowledge which has confirmed the view of Claude Bernard on the supreme physiological importance of his *milieu intérieur.* There are the diverse products of the pharmacological laboratories, where molecules are made to do the bidding of the research-worker.

PSYCHOLOGY

Finally, in my work in Edinburgh I have had so much help from psychologists that it would be ungrateful not to add to my list the better understanding which they have given to us of the immediate clinical importance of the mental processes of surgical patients, a matter partly dealt with in the memorable address of the last Lister Orator (Jefferson 1949).

Lister's Achievement and its Lesson

These then are some of our present debts to the fundamental sciences, and bewildering they are in both number and complexity. Fortunately we know Lister's personal views on the relative importance of contributions to surgery, and to these I shall return.

First, since it is the pious duty of each Orator to pay his humble tribute to the memory of Lister, I must try to decide the way in which we, his debtors, should measure his achievements. Bacon proposed one standard:

> "If a man perform that which hath not been attempted before, or attempted and given over, or hath been achieved but not with so good circumstance, he shall purchase (= acquire) more honour than by effecting a matter of greater difficulty or virtue wherein he is but a follower."

This concept sets a standard of perseverance, and of craftsmanship which in surgery includes much more than mere manual dexterity; and measured by it there can be no doubt of Lister's place in surgery. But the standard cannot be used as the sole measure of Lister's achievement: his contributions ranged far beyond surgical craftsmanship, to a surgical principle.

Now the value of a principle is the greater the larger the number of problems to whose treatment it can be applied. Upon a comprehensive principle it is not possible to put a precise value: one might as well try to measure an emotion or an abstraction. There are few principles in any of the sciences as fundamental as is that of Lister in surgery, for it is applicable to every problem involving the deliberate making of a wound, and to every problem involving the prevention or eradication of infection in a wound. In making this statement I give no weight to the rather tawdry attempts which have been made to separate the "antiseptic" from the "aseptic" era. Those who try to do so have not studied Lister's papers: for example, his statement that "The part to be operated upon, then, being in an *antiseptic* atmosphere, if the finger is to be introduced into the wound . . . you must take special care that it is an *aseptic* finger." But even great principles must conform to one rule: they must be adaptable to changes in every related part of the whole body of knowledge. It is one of the glories of Lister that he realised the need for this constant adjustment of his principle, and that he communicated these adjustments to medical literature when he thought it timely. By this standard also his work was and is supreme.

It is therefore of great interest, and to my mind of compelling present importance, that there is indisputable evidence that these were not the standards by which Lister judged his own contributions to surgery. Towards the end of his public life and while still in full possession of his great intellectual powers, he remarked to the late

Professor Bulloch that if his works were read after his death, the papers most highly thought of would be that on the early stages of inflammation and that on the cutaneous pigmentary system of the frog. With universal agreement, Lister might have singled out his records of practical achievements: yet he chose papers in those fundamental sciences to which he had purposefully devoted himself while preparing for his life's work.

This Listerian ordering of values might well command the attention of those who are concerned with the training of the surgeons of the future. Lister would not have taken long to decide between on the one hand the opportunity of obtaining a knowledge of the preclinical sciences from textbooks or in the lecture-room, and on the other the opportunity of a period spent in the discipline of a laboratory, which included at least observation of research and at best active participation in it. I feel sure that Lister would have counselled that any policy of "staffing and training" which made it difficult or impossible to secure for recruits to surgery a training such as he himself had, would be imperilling the future of British surgery.

A great many surgeons can do what is at present wanted, and honourable and useful lives they lead. The training of at least a proportion of the surgeons of the future should be such that they have given some thought to what will be wanted before their professional lives are over. The next generation will see profound changes in surgical practice. The early advent of these and their intelligent use depend upon the early introduction and continued application to the ancillary sciences of young men now in training. Moreover, the Listerian outlook might perhaps influence, more often than it does, the present decisions of those whose duty it is to select from among many applicants surgeons to fill senior positions. Bacon stated the general principle to be used in making any senior appointment: "... expert men can execute, and perhaps judge of particulars, one by one: but the general counsels, and the plots and marshalling of affairs come best from those that are learned."

Within recent months the general problem of the scientific approach to medicine has been considered in addresses by the President of the Royal Society and the Secretary of the Medical Research Council; and it would be idle for me to recapitulate arguments which have the weight of their authority.

I believe that in training the surgeons of the future the attempt should be made to ensure that all are alive to the possible applications of advances in the related sciences: surgeons who do not possess this understanding will lack purpose. It would be wasteful and wrong to attempt to place upon surgeons the entire responsibility for making these applications; often they are matters of technology or even of production, which are not the surgeon's provinces. Nor is it necessary for each surgeon to be completely expert in all or even in any one of the ancillary sciences: his early training rarely provides an adequate basis for this, and in my experience a young physicist (for example) will quickly learn the physiological bases of problems in the solution of which he may be required to help. Indeed other scientists distrust doctors. "In designing a medical instrument," writes the biophysicist Stacy, "one makes it foolproof, then goes further to make it nurseproof. It is difficult to make the instrument doctorproof, for a doctor may carry a screwdriver in his pocket." Although it was written in jest—or at least one hopes so—there is possibly enough truth in this opinion to warn us surgeons, in this year of 1952, to pay more heed to our knowledge of the related sciences. I believe that their challenge should be met: how would it be best to do so?

The fundamental problem is to secure the acceptance by every citizen, medical and lay, of the proposition that the research of today, whether carried out in laboratory or in ward, is often the life-saving clinical care of to-morrow. This Lister knew, and for this he lived. In present circumstances, I believe that the many and complex problems still facing surgeons can best be approached in university hospitals; the clinical staffs of these should not be limited by a rigid establishment. The staff and wards of such a hospital should form with the staff and buildings of the university departments of all other related disciplines a single intellectual and geographical unit. Every contributor to this common weal—clinician, preclinician, and ancillary scientist—would be pledged, as was Lister, not to disease but to the patient. Here the sick would be tended with the broadest possible background of human relationships. Here every idea would be seminal. Here every idea might fructify a host of others. Here after proper trial in laboratory or ward every idea would find either ready application or quick rejection. Here would be the form of memorial that Lister would have thought best and liked best.

* * *

"*The History of the world*," wrote *Thomas Carlyle*, "is but the Biography of great men." However wide his perspective, however sweeping his range, each future historian must find a place for Joseph Lister. Lister, whose life's work changed for all time the lot of the surgically afflicted. Lister, whose life's work left us a shining beacon towards which each one of us may strive. Our Lister, to whom with thankful hearts and with gratitude for our heritage this day we pay our homage.

REFERENCES

Florey, H. W. (1945) *Brit. med. J.* ii, 635.
Jefferson, G. (1949) *Ibid*, i, 1105.
Muir, R. (1933) *Canad. med. Ass. J.* 29, 349.

CŒLIAC DISEASE: GASTRO-INTESTINAL STUDIES AND THE EFFECT OF DIETARY WHEAT FLOUR

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As a result of observations made in Holland, Dicke (1950) showed that patients with cœliac disease improved when wheat and rye flour were excluded from their diet. Weijers and van de Kamer (1950) demonstrated that there was a decrease in the fæcal fat under these circumstances and that the reintroduction of wheat flour, though not of wheat starch, into the diet led to deterioration.

The object of the studies reported in this paper was to establish the nature of the alteration in gastro-intestinal function in cœliac disease and to study the effect of dietary wheat flour on the syndrome.

Many different interpretations have been placed on the biochemical findings in cœliac disease. Methods have been developed in the study of adult idiopathic steatorrhœa which have defined the biochemical features of the condition (Frazer 1951) and the first part of this investigation consists of the application of these methods to cœliac disease. The second part concerns the influence of wheat on the clinical condition and intestinal function.

Gastro-intestinal Function

Ten cases of cœliac disease, diagnosed on clinical, biochemical, and radiological evidence, were studied while on normal hospital diet (diet A).

METHODS

Assessment of fæcal fat.—The fæcal fat was measured by the daily fatty-acid method adapted from that described by Kamer et al. (1949). The patients received 40 or 50 g. of fat per day and the stools were collected daily.

Each 24-hour stool collection was made up to 1 litre with water and mechanically mixed for 1 min. A 10 ml. aliquot of the fæcal emulsion was saponified with 47 ml. of an alcoholic 3% KOH solution containing 0·4% amyl alcohol. The saponified mixture was cooled and acidified with HCl, and 50 ml. of petroleum ether added. The mixture was shaken well for 1 min. and allowed to settle.

A 10 ml. aliquot of the petroleum ether layer, to which a few drops of absolute alcohol had been added, was titrated with 0·1 *N* alcoholic soda or tetramethylammonium hydroxide, using thymol blue as indicator. The results were expressed as grammes of stearic acid. The daily totals of fæcal fatty acid were converted to 3-day sliding means and adjusted where necessary to correspond to a 40 or 50 g. fat intake.

Pancreatic enzymes.—Amylase, lipase, and trypsin were estimated in duodenal juice withdrawn by intubation.

Amylase was measured by the method of Ågren and Lagerlöf (1936), using soluble starch as substrate.

For lipase 1 ml. of olive oil was added to 5 ml. of phosphate buffer containing 0·5% bile salts at pH 7·8 in a 50 ml. stoppered conical flask. 0·1 ml. of duodenal juice was added and the mixture shaken for 30 min. at 37°C. It was then acidified and extracted with 20 ml. of benzene. A 10 ml. aliquot of the upper benzene layer was titrated with 0·1 *N* tetramethylammonium hydroxide in alcohol (Frazer, Sammons, and Thompson 1952).

For trypsin the method of Charney and Tomarelli (1947), with sulphanilamide azocasein as substrate, was used. The digestion was estimated colorimetrically.

Systemic hyperlipæmia.—10–20 g. of fat was given orally to the fasting child, and during the next five hours systemic hyperlipæmia was studied by means of the chylomicrograph technique (Frazer and Stewart 1939).

Absorption in the upper small intestine.—This may be measured in adults by a study of blood-glucose levels after the gradual administration of an isotonic glucose solution intraduodenally (Frazer, French, Thomas, and Thompson 1952). Oral glucose tests may give occasional false results because of variable gastric emptying, though they give some information about intestinal function. Only oral glucose tests were possible on our patients; 15–30 g. of glucose was given, the dose depending on body-weight, and the blood-sugar was estimated over a 3-hour period by the Hagedorn-Jensen method. The same dose was used throughout for any one child.

Radiography of the upper small intestine.—Examination of the intestinal tract was carried out with both flocculable and non-flocculating suspensions of barium sulphate, with particular reference to the small-intestine pattern (Astley and French 1951).

RESULTS

Clinical Assessment

The condition of the ten children conformed to the generally recognised clinical pattern of cœliac disease. About the first birthday, after a normal and uneventful infancy, a disinclination for food was associated with an insidious change in bowel habit. The stools gradually increased in frequency and became pale, bulky, and offensive. There was a steadily increasing anorexia, sometimes combined with vomiting, and the weight became stationary or decreased. In severe cases with emaciation, abdominal distension contrasted with considerable wasting of the buttocks and the limbs. At the same time a happy and contented infant slowly developed into a fractious, morose, apathetic, and extremely difficult child, well-nigh impossible to interest or satisfy. These striking changes in behaviour mirrored the physical and nutritional state and were one of the fundamental clinical features of the disorder. The clinical findings did not differ from those generally recognised in cœliac disease (Parsons 1932).

Biochemical and Radiological Assessment (see table I).

Fæcal fat.—The amount of fat in the stools of normal children taking 40 g. of fat per day averages 2 g. daily, and does not exceed 4 g. In all our cœliac cases the fæcal fat output was increased above normal on a standard intake. In seven cases daily fat-balances were carried out throughout their stay in hospital; they showed considerable variation in the fæcal output from day to day. In each case the figures quoted represent the average of a 10-day balance. It is realised that the fæcal fat may not be derived entirely from unabsorbed dietary residues. Other possible sources are cellular debris, excreted fat, and fat synthesised by intestinal organisms. In the patients we have so far investigated most of the fæcal fat appeared to be of dietary origin, since parallel changes occurred when the dietary fat was removed and reintroduced. Some increase of bacterial fat is to be expected in cœliac disease, however, because of the increased bacterial content of the stools.

Pancreatic enzymes.—In normal children over one year of age, amylase, lipase, and trypsin are always present; amylase may be deficient under this age. The normal ranges by the methods used are: amylase 2–8 units, lipase 2–6 units, trypsin 8–50 units. All the cœliac children showed normal levels of the three enzymes, with the exception of the two youngest, who showed slightly subnormal levels of amylase only, lipase and trypsin being normal.

TABLE I—RESULTS OF INVESTIGATION OF TEN CASES OF CŒLIAC DISEASE ON DIET A (WHEAT-FLOUR-CONTAINING)

Case no.	1	2	3	4	5	6	7	8	9	10	Average	Normal
Age (years)	3	3	2¼	6	4	1½	¾	6	3½	1¼	3	—
Fæcal fat (g. per day)	15·2	12·0	10·4	8·0	20·0	10·0	6·4	6	6	9	10·3	<4
Pancreatic Enzymes	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	..	..
Chylomicrograph (maximum increment in particles per field.. ..	65	40	130	57	16	60	61	65	82	17	59	>150
Oral glucose (maximum increment in mg. per 100 ml.)	34	0	26	26	11	30	21	25	11	18	20	>40
Radiograph (water suspension) ..	F + + +	F + + +	F + + +	F + + +	F + + +	F + + +	Not examined	F + + +	Not examined	F + + +	..	..
Radiography (non-flocculable suspension)	D + + +	D + + +	D + + +	D + + +	D + + +	D + + +	D + + +	D + + +	D +	D + + +	..	..

F = flocculation pattern seen with water suspension of barium sulphate.
D = wide dilated pattern seen with non-flocculable barium sulphate suspension

Chylomicrographs.—In healthy children the maximum increment in the chylomicron count exceeds 150 particles per standard field 2–3 hours after the meal. In all our cases the rise in chylomicron count was delayed and depressed. The average maximum increment was 59 and the range was 16–130.

Oral glucose-tolerance tests.—The usually accepted increment in normal children exceeds 40 mg. of glucose per 100 ml. of blood. In the cœliac cases, the average was 20 mg. per 100 ml. (range 0–34). Thus all glucose-tolerance curves were flattened.

Small-intestine radiography.—In normal adults contrast radiography with both flocculable and non-flocculating media, shows a fine feathery mucosal pattern. In adults with the sprue syndrome, simple flocculable suspensions of barium sulphate give a clumped or flocculated appearance which is evidence of an increase in mucus secretion (Frazer, French, and Thompson 1949). Examination of such cases with non-flocculating suspensions shows a wide dilated small-intestine pattern (Ardran, French, and Mucklow 1950).

In normal children simple suspensions give a feathery mucosal pattern less often than in adults, the barium often presenting a clumped appearance (Zwerling and Nelson 1943). A more feathery appearance is seen with the non-flocculating suspension (Astley and French 1951).

In the eight cœliac children examined with the simple suspension a flocculated appearance was invariably seen in the small intestine; the non-flocculating suspension showed a wide dilated appearance similar to that in the adult sprue syndrome, the feathery appearance of the mucosa being absent. These results are to be reported in detail elsewhere. The difference between the normal intestine and the dilated appearance observed in these cases is shown in figs. 1 and 2.

CONCLUSION

From these observations it would appear that the changes in gastro-intestinal function are identical with those of adult idiopathic steatorrhœa.

The Effect of Wheat Flour

METHOD

After completing these basic studies, we investigated the influence of wheat in two stages: (1) by placing the child on an entirely wheat-free diet (diet B); and (2) by the reintroduction of wheat flour, wheat starch, or wheat gluten into the diet. The effects were assessed by repeating the gastro-intestinal studies and by clinical observation of the remissions and exacerbations induced by changes in diet.

Diet containing Wheat Flour (Diet A)

Diet A was the normal hospital diet containing the usual starchy foods, and corresponded to a daily intake of 60–80 g. of wheat flour.

Diet free from Wheat Flour (Diet B)

Diet B was the normal hospital diet modified by the substitution of cornflour and/or soya flour, for wheat flour, the latter being entirely excluded.

Fat-content (40 or 50 g. daily depending on age) was controlled throughout in all the diets; carbohydrate and protein were approximately 150 g. and 45 g. daily respectively. The cornflour or soya flour was made into biscuits to replace bread. In young or very sick children a high calorie milk mixture, thickened with cornflour, was used instead of biscuits.

TABLE II—DIFFERENCE IN FÆCAL FAT ON DIET A AND DIET B

Case no.		1	2	3	4	5	6	7	Mean
Fæcal fat (g. per day)	Diet A (normal)	15·2	12·0	10·4	8·0	20·0	10·0	6·4	11·7
	Diet B (wheat-free)	2·0	3·2	3·2	2·4	6·8	2·8	4·0	3·5

Figures in each case are the average of 10 consecutive days. Fat intake 40 g. per day (50 g. in cases 4 and 6).

Wheat Starch and Gluten Fractions

The wheat starch and gluten fractions were prepared for us by Energen Foods Co. from Canadian spring wheat. The flours were untreated and unbleached, and had no vitamin or calcium additions. A dough of normal consistence was made with water and 1·5% sodium chloride. The salt was included to facilitate the removal of soluble proteins. No yeast, raising ingredients, or other additives were included. After standing for half an hour, the dough was kneaded under water for an hour, while the starch was extracted in suspension. The water was replaced at intervals. The resulting gluten mass was dried in a high vacuum at a maximum temperature of 60°C. It was then broken down and ground to a 60 mesh. The final protein-content was 80%.

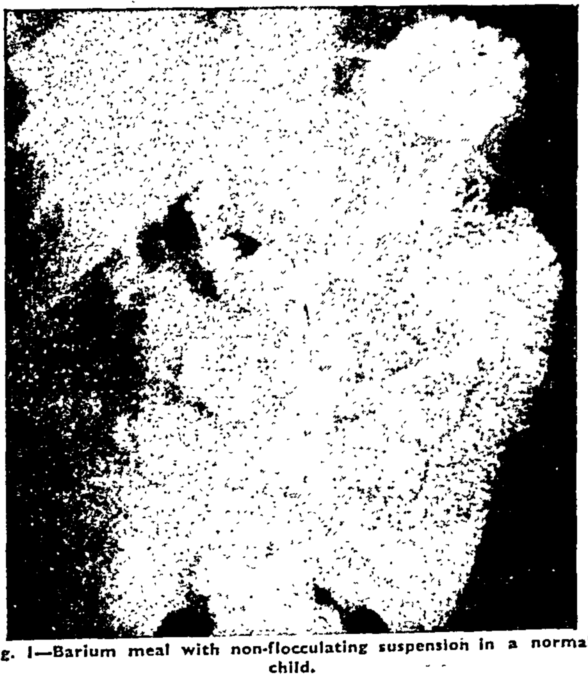

Fig. 1—Barium meal with non-flocculating suspension in a normal child.

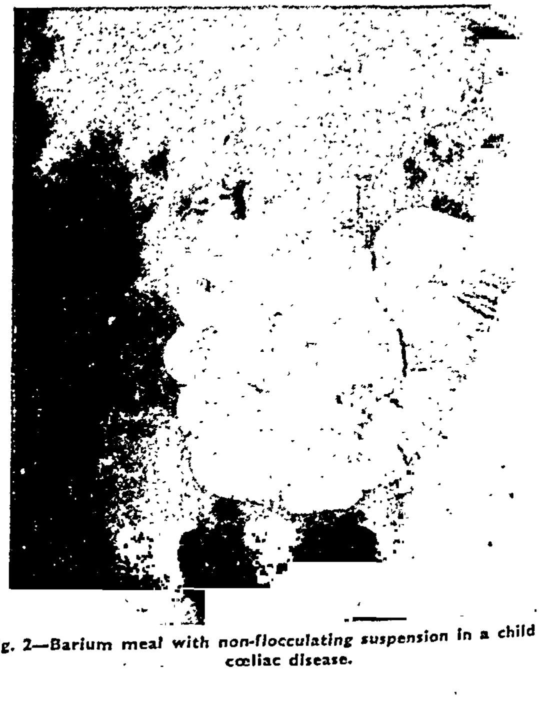

Fig. 2—Barium meal with non-flocculating suspension in a child with cœliac disease.

TABLE III—COMPARISON OF FINDINGS IN SEVEN CASES OF CŒLIAC DISEASE ON DIET A (WHEAT-FLOUR-CONTAINING) AND DIET B (WHEAT-FLOUR-FREE)

Case no.		1	2	3	4	5	6	7
Chylomicrograph ..	Diet A	flat	flat	sub-normal	flat	flat	flat	flat
	Diet B	normal	normal	normal	normal	improved	normal	normal
Oral glucose tolerance ..	Diet A	flat	flat	flat	flat	flat	flat	flat
	Diet B	normal	almost normal	normal	almost normal	improved	normal	improved
Small intestine radiography (non-flocculable suspension)	Diet A	dilated	dilated	dilated	dilated	dilated	dilated	dilated
	Diet B	normal	improved	improved	almost normal	dilated	normal	normal

RESULTS

Exclusion of Wheat Flour from the Diet

All the children improved clinically when placed on the wheat-free diet. In 2–3 weeks there was a marked change: they ate more, gained in weight, and lost their irritability; the diarrhœa diminished and in most cases the stools became darker and formed.

The seven children who had been maintained on a continuous fat-balance were reinvestigated.

Within 30–50 days fat-balances showed the disappearance of excessive fat from the stools. Table II shows that in six out of the seven children the fæcal fat returned to normal levels on diet B. The seventh case showed a marked improvement, but the fæcal fat level was still above normal.

Chylomicrographs, glucose tolerance, and small-intestine radiography showed commensurate improvement, though return to normal was not always as rapid as in the case of the fæcal fat (table III).

Reintroduction of Wheat Flour, Starch, or Gluten

Wheat flour.—After a period on the wheat-flour-free diet, during which the fæcal fat output fell to within normal limits and general recovery took place, reintroduction experiments were begun. It was found that the inclusion of 60–80 g. wheat flour per day resulted in rapid deterioration. Within 1–3 weeks there was a loss of appetite, sometimes associated with vomiting, diarrhœa returned, there was a change of temperament, and the children began to lose weight. The continuous fat-balances showed that the return of the diarrhœa was soon associated with excessive fæcal fat.

Two patients were treated in this way, and deterioration was induced on two occasions in each. In the second phase of deterioration, non-agenised flour was used. One case is reported in full below (case 1).

Wheat starch.—In view of the observations of Weijers and van de Kamer (1950) that wheat starch did not cause deterioration in cœliac disease, it was decided to study the effect of the starch fraction on children already ill on diet A. Two children were fed with 80 g. daily of pure wheat starch in the form of biscuits. All other forms of wheat were excluded from the diet. Improvement took place comparable with that obtained on diet B (case 1). This suggested that the factor causing deterioration was confined to the gluten fraction. Wheat starch was therefore included in the otherwise wheat-free diet, for it made the biscuits more palatable and of a better texture.

Wheat gluten.—A suspension of wheat gluten in water was given to three children already in remission on diet B. The quantity used was roughly equivalent to the amount of gluten present in the basic wheat-flour diet. Within 1–3 weeks, deterioration took place in exactly the same way as when wheat flour was given. The recrudescence of diarrhœa was again associated with an increase in fæcal fat, and chylomicrographs and small-intestine pattern also showed a reversal towards the initial state. When gluten was omitted, recovery again occurred. The results in these three cases are reported in detail below (cases 2, 3, and 4).

Controls.—Six normal children in the same age-group had a similar quantity of gluten added to their normal diet for 3 weeks, with no change in appetite, demeanour, or bowel habits. Fæcal fat output was measured in two cases, and showed no increase during the feeding of gluten.

CASE-RECORDS

Case 1.—A girl, aged 3, had been ill for 9 months with diarrhœa, intermittent vomiting, and progressive emaciation. She weighed 16 lb. (fig. 3*a*) and was unable to stand. The results of gastro-intestinal function tests on diet A are shown in table I.

She was placed on diet B and vomiting, diarrhœa, and anorexia disappeared within 2 weeks. The stools became formed and less frequent. She gained 10 lb. in 10 weeks. The daily fæcal fat, chylomicrograph, oral glucose tolerance, and X-ray appearances returned to normal.

The change in her appearance 9 months later is shown in fig. 3*b*.

After she had been on diet B for 3 months, wheat flour was again introduced into the diet. The 220-day fat-balance (fig. 4) shows the increase in fæcal fat which followed. Anorexia, vomiting, diarrhœa, and abdominal distension returned. When the wheat flour was replaced by wheat starch, which forms about 90% of the wheat flour, there was a gradual return to normal fæcal fat levels and a steady improvement in the child's condition, similar to that observed on diet B. Wheat flour was again added to the diet and an increase in

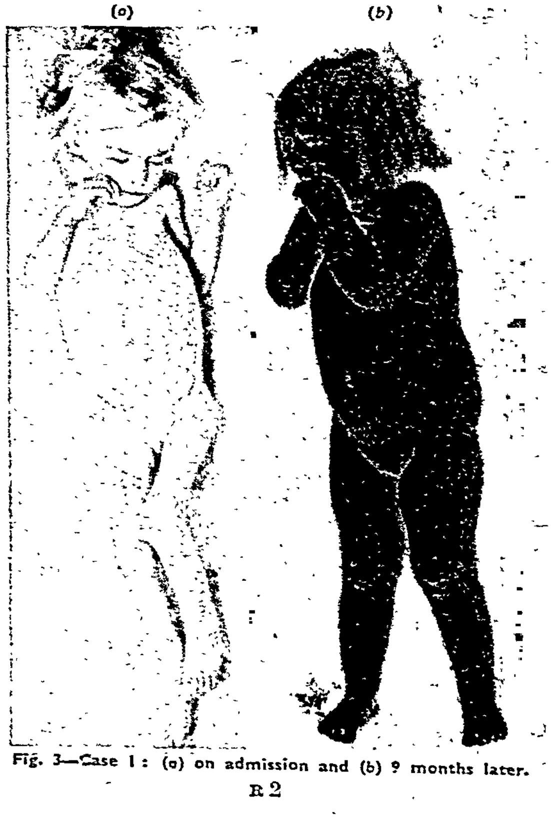

Fig. 3—Case 1: (a) on admission and (b) 9 months later.

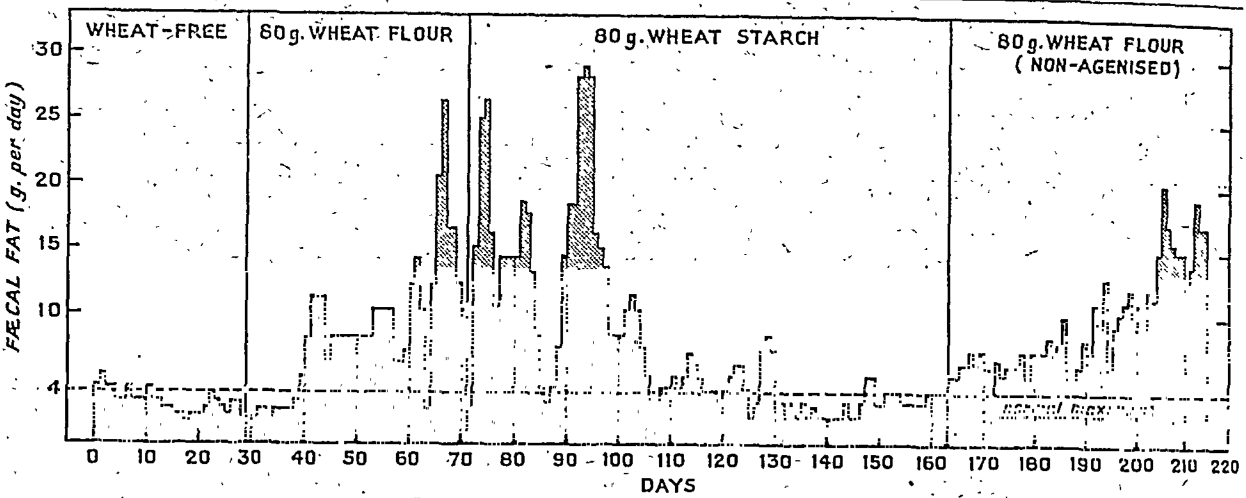

Fig. 4—Continuous fat-balance in case 1 on 40 g. of fat daily, showing rise in fæcal fat on introduction of wheat flour and fall to normal after substitution of wheat starch.

fæcal fat and general deterioration again occurred. On the second occasion the wheat flour used was non-agenised.

Case 2.—A girl, aged 3, had a history of diarrhœa, occasional vomiting, loss of weight, and increasing protuberance of the abdomen for 11 months. She weighed 25 lb. and had the classical appearances of cœliac disease (fig. 5*a*). Her gastro-intestinal function showed the usual changes (table I).

On diet B her appetite increased within a week and vomiting ceased. In the 2nd week diarrhœa ceased and the stools became darker; after 3 weeks she had only one stool a day, semi-formed, and normal in size and colour. The decrease of fæcal fat and increase of body-weight are shown in fig. 6. After 6 weeks on diet B the daily fæcal fat had fallen to 3·2 g., the chylomicrograph maximum increment had risen to 170 particles per field, and the oral glucose maximum increment was 39 mg. per 100 ml. Radiographic examination of her upper small intestine showed much improvement, but the pattern was still abnormal. These investigations showed that she had almost returned to normal after 6 weeks on *diet B*. *The change in her appearance* after 7 weeks on this diet is shown in fig. 5*b*.

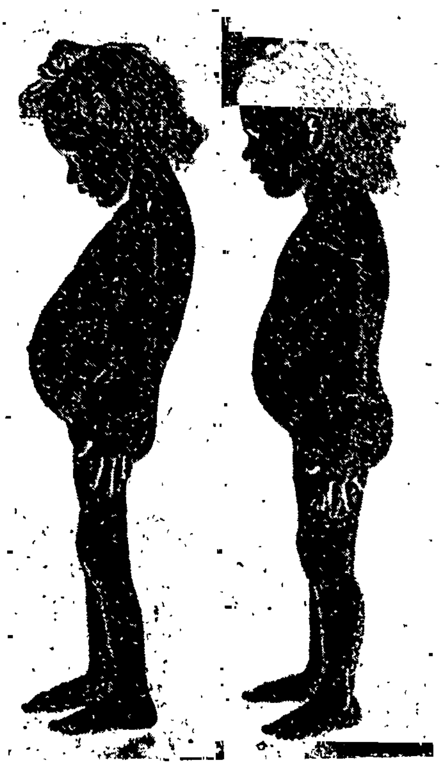

Fig. 5—Case 2: (*a*) on admission and (*b*) 3 months later after 7 weeks on wheat-free diet.

She was then given gluten in divided doses totalling 9 g. per day. Within 3 days her appetite decreased and she became more irritable. After a week she began to vomit occasionally, the stools became paler, and their fat-content increased. Within 2 weeks the fæcal fat was clearly abnormal (fig. 6), she had lost $1^1/_2$ lb. in weight, and the stools were now becoming loose and bulky. The gluten was withdrawn and the child's condition again improved.

Case 3.—A girl, aged $2^1/_4$, had passed offensive, bulky stools for 1 year. She was emaciated with a protuberant abdomen and unhappy disposition. She weighed 20 lb. (fig. 7*a*). Table I shows the results of gastro-intestinal investigation.

On diet B her appetite and temperament soon improved, and the fæcal fat decreased (fig. 8). Reinvestigation showed: daily fæcal fat 3·2 g., chylomicrograph maximum increment 300 particles per field, and oral glucose maximum increment 90 mg. per 100 ml. Radiography showed some improvement, but the intestinal pattern was still definitely abnormal.

Her appearance 6 months after admission is shown in fig. 7*b*.

Fig. 8 shows an increase of fæcal fat after the child had been on diet B for about 3 weeks. This was associated with a coryza and has been seen in other cœliac children on continuous fat-balances.

When 9 g. of wheat gluten was added to her daily diet, the fæcal fat began to increase (fig. 8), and anorexia, occasional vomiting, and loose stools returned. She began to lose weight. On withdrawing the gluten the child recovered.

Case 4.—A boy, aged 6, had been treated for 3 years on a low-fat diet, and was progressing moderately well. However,

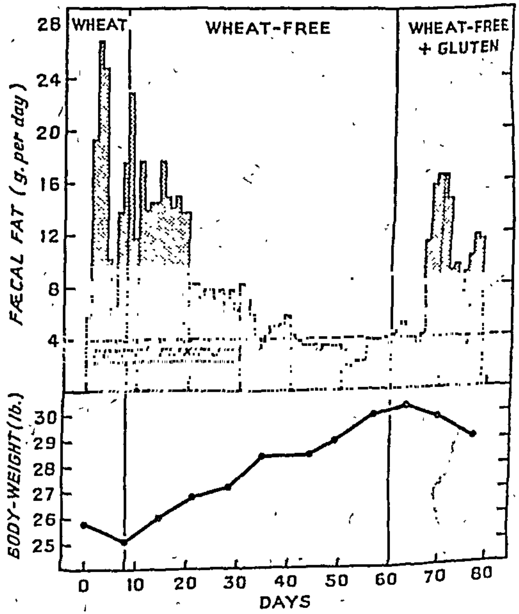

Fig. 6—Continuous fat-balance in case 2 on 40 g. of fat daily, showing fall in fæcal fat and rise in weight on wheat-free diet, followed by deterioration on gluten.

he still had two to three loose stools daily, he was rather undersized, and had a protuberant abdomen. The results of investigation on diet A are shown in table I.

On diet B the fæcal fat fell to normal within 2 weeks (fig. 9) and he had only one formed stool daily. In 5 weeks on diet B he gained 3½ lb.; during the preceding 5 weeks he had gained only 1 lb. In the 4th week on diet B daily fæcal fat was 24 g., chylomicrograph maximum increment 250 particles per field, and oral glucose maximum increment 37 mg. per 100 ml. The radiographic appearance of the small intestine was much improved, but not quite normal.

He was then given 12 g. of gluten per day. After 3–4 days his appetite diminished, in a week he developed profuse, watery diarrhœa, and in 2 weeks fæcal fat had increased. A week later gluten was withdrawn and there was gradual improvement in appetite and diarrhœa (fig. 9).

Discussion

As children with cœliac disease apparently show the same radiological changes in the small intestine and the same biochemical abnormalities as adults with idiopathic steatorrhœa, it seems likely that they suffer from the same defect of absorption in the upper intestine, probably affecting all substances.

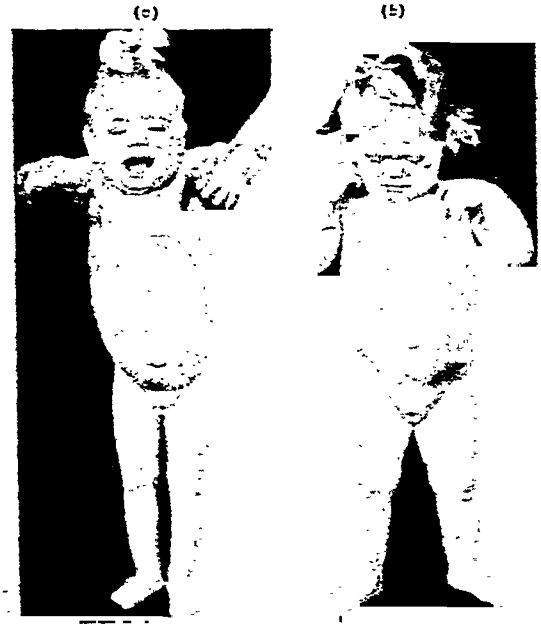

Fig. 7—Case 3: (a) on admission and (b) 6 months later.

On the normal hospital diet there was a big increase in fæcal fat in all our cases, and although this may not be entirely of dietary origin, the evidence suggests that most of the fat came from the diet and that it indicated an absorption defect. It seems likely that fat is normally digested and prepared for absorption by fine emulsification, but that absorption of particulate fat is delayed and depressed, as shown by the chylomicrographs.

The glucose-tolerance curves are also compatible with an absorption defect for recent work has shown that the low curves in adult idiopathic steatorrhœa are associated with a defect in the absorption of all substances (Frazer, French, Thomas, and Thompson 1952). The absorption defect may possibly be due to excessive mucus secretion or lack of intestinal motility, as suggested by the radiological findings, or to both. Excessive bacterial activity in the upper small intestine may be related to these abnormalities.

The investigation of our patients showed that the striking clinical improvement on wheat-free diet was accompanied by parallel increase in the absorption of fat. This confirms the original observations of Dicke (1950) and the later studies of Weijers and van de Kamer (1950) on the beneficial effect of excluding wheat and rye flour from the diet of cœliac children. The radiographic appearances of the small intestine and the absorption of glucose and particulate fat also became more normal, suggesting that all absorption had improved.

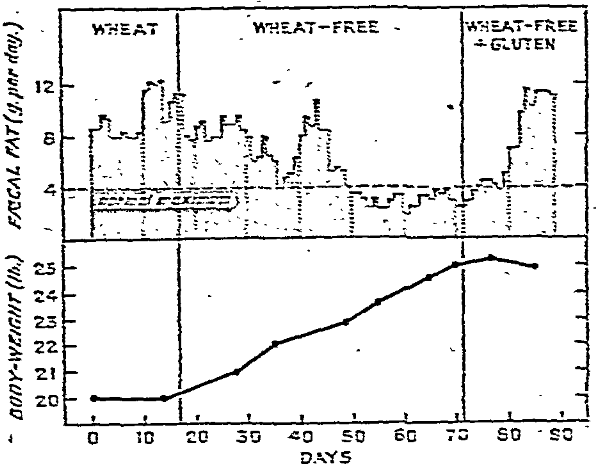

Fig. 8—Continuous fat-balance in case 3, on 40 g. of fat daily, showing fall in fæcal fat and rise in weight on wheat-free diet, followed by deterioration on gluten.

The effect of reintroducing wheat flour or wheat gluten makes it quite clear that wheat causes deterioration in cœliac children, but not in normal children. Agenisation of the wheat flour seems to play no part in this. Wheat starch does not have the same action as wheat flour, showing that it is not the starch itself which is harmful: in fact children on a relatively high total intake of starch improved rapidly. Many previous workers have reported that starches have a deleterious effect in cœliac disease, and claimed that their removal from the diet was essential to clinical improvement. In the diets recommended in these reports, however, the removal of starches was synonymous with the removal of wheat flour (Howland 1921, Sauer 1925, Haas 1938, Andersen 1947, Sheldon 1949, May and Lowe 1951). The improvement recorded in these reports, was not so much due to the strict removal of all starches as to the fact that their removal entailed the exclusion of wheat gluten.

Our present studies indicate that even in the early stages of treatment there is no need to restrict carbohydrate or even fat: an almost unlimited choice of food may be made provided that wheat and rye flour are excluded. A high caloric diet may be given throughout, with biscuits made from cornflour, soya flour, or wheat starch instead of bread. All the children sent home on this diet have so far remained in normal health. The

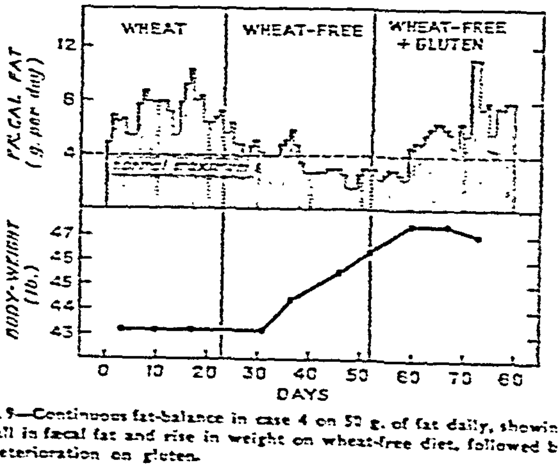

Fig. 9—Continuous fat-balance in case 4 on 50 g. of fat daily, showing fall in fæcal fat and rise in weight on wheat-free diet, followed by deterioration on gluten.

dietary control of cœliac disease has thus been much simplified.

The precise way in which the gluten fraction disturbs gastro-intestinal function in cœliac disease is being further investigated.

Summary

Gastro-intestinal function was investigated in ten children with cœliac disease. The changes were very similar to those in adult idiopathic steatorrhœa.

The removal of wheat flour from the diet resulted in rapid improvement, both clinically and biochemically. Deterioration followed the reintroduction into the diet of wheat flour or wheat gluten, but wheat starch had no harmful effect.

This work has been carried out in close collaboration with Prof. H. ten Bokkel Huinink, Dr. H. A. Weijers, and Dr. J. H. van de Kamer of Utrecht to whom we are much indebted.

We wish to thank Sister N. Howells and the nursing staff at the Children's Hospital, Birmingham, for their invaluable help with the metabolic studies. We are also indebted to Dr. Frances Braid for allowing us to investigate case 10, to Dr. R. Astley for the radiographic studies, to Miss E. M. Hickmans for the glucose tests, to Mr. John Taylor and Mr. Roy Powditch for technical assistance with the daily fæcal-fatty-acid estimations, to Mr. G. A. Rowe and Mr. J. G. Williamson for the photographs, to Mr. A. Wilkinson of Energen Foods Co. and Dr. R. D. Firth for providing us with wheat starch and gluten. Finally, we gratefully acknowledge financial assistance from the United Birmingham Hospitals Research Fund, the Sir Halley Stewart Trust, and the Medical Research Council.

REFERENCES

Ågren, D. Lagerlöf, I. (1936) *Acta. med. scand.* 90, 1.
Anderson, D. H. (1947) *J. Pediat.* **30**, 564.
Ardran, G. M., French, J. M., Mucklow, E. H. (1950) *Brit. J. Radiol.* **23**, 697.
Astley, R., French, J. M. (1951) *Ibid*, **24**, 321.
Charney, J., Tomarelli, R. M. (1947) *J. biol. Chem.* **171**, 501.
Dicke, W. K. (1950) Coeliakie. Utrecht M.D. thesis.
Frazer, A. C. (1951) *In* Modern Trends in Pædiatrics. London.
— French, J. M., Thompson, M. D. (1949) *Brit. J. Radiol.* **22**, 123.
— — Thomas, G., Thompson, M. D. (1952) *Clin. Sci.* **11**, 141.
— Sammons, H. G., Thompson, M. D. (1952) To be published.
— Stewart, H. C. (1939) *J. Physiol.* **95**, 21P, 23P.
Haas, S. V. (1938) *J. Pediat.* **13**, 390.
Howland, J. (1921) *Trans. Amer. pediat. Soc.* **11**, 15.
Kamer, J. H. van de, Bokkel Huinink, H. ten, Weijers, H. A. (1949) *J. biol. Chem.* **177**, 347.
May, C. D., Lowe, C. U. (1951) *Amer. J. Dis. Child.* **81**, 81.
Parsons, L. G. (1932) *Ibid*, **43**, 1293.
Sauer, L. W. (1925) *Ibid*, **29**, 155.
Sheldon, W. (1949) *Arch. Dis. Childh.* **24**, 81.
Weijers, H. A., Kamer, J. H. van de (1950). Fat Absorption in

Zwerling, H., Nelson, W. E. (1943) *Radiology*, **60**, 277.

NEPHROSIS TREATED BY MALARIA

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It has long been known that in nephrosis—type-II nephritis of Ellis (1942)—a remission may sometimes be initiated by one or other of a variety of agents such as infections, particularly measles, infusions of plasma, large doses of urea, or large doses of salts such as potassium citrate. More recently A.C.T.H. has been added to this list (Barnett et al. 1950, Riley 1950). Sometimes the remissions provoked by these means have proved long-lasting and amount to cures.

After experiencing the occasionally dramatic effect of measles on nephrosis, as well as the difficulties and dangers of this form of treatment, it seemed sensible to look for an acute infection which might have a therapeutic effect similar to measles but could be easily induced and easily controlled. It was decided to try whether malaria would fulfil this need. Four patients with the nephrotic syndrome have been infected with malaria to date, in two with dramatic effect, and in two with no such effect (one of the latter proved to have type-I nephritis).

CASE-RECORDS

Case 1.—A girl, aged 5 years, developed generalised œdema in January, 1948. There had been no preceding sore throat or other infection. During the next nine months, spent in various hospitals, she remained constantly œdematous.

On admission in September, 1948, she had generalised œdema with gross ascites; blood-pressure 135/85 mm. Hg, retinal vessels normal. Her urine contained albumin, a few red cells, and granular casts. The plasma-albumin level was 1·2 g. per 100 ml., plasma-globulin level 3·1 g. per 100 ml., plasma-cholesterol level 550 mg. per 100 ml., blood-urea level 26 mg. per 100 ml.

Progress.—During the next four months the patient's condition remained the same; on eight occasions ascitic fluid in amounts of about 3 litres was removed. On two occasions the skin of the legs was incised and about 7 litres of œdema fluid drained off. In addition the following treatments were successively applied, but without effect: (1) high-protein salt-free diet; (2) mercurial diuretic ('Novurit') 1 ml. intramuscularly on alternate days for five doses; and (3) urea 30 g. daily for seven days.

Malaria Therapy.—On Jan. 12, 1949, malarial mosquitoes were applied. These, as also in the subsequent cases, were *Anopheles atroparvus* infected with *P. vivax*, Madagascar strain. On Jan. 18 the patient still had generalised œdema with ascites; her blood-pressure was 120/75 mm. Hg; and her urine contained a moderate amount of albumin and occasional red cells, but no casts. Her plasma-albumin level was 1·0 g. per 100 ml., plasma-globulin level 2·6 g. per 100 ml., non-protein nitrogen level 28 mg. per 100 ml., and plasma-cholesterol level 750 mg. per 100 ml. On Jan. 24 malarial fever began, the temperature rising to 102°F. Next day diuresis set in and œdema began to subside rapidly, disappearing completely by Feb. 2, ten days from the onset of fever. In this period the patient lost 18 lb., bringing her weight to 42 lb. Her urine now contained less albumin, and the blood chemistry was returning to normal; on Feb. 9 the plasma-albumin level was 2·4 g. per 100 ml., plasma-globulin level 4·6 g. per 100 ml., and plasma-cholesterol level 200 mg. per 100 ml. The malarial fever was at first quotidian. On the third day 'Thio-bismol' 0·2 g. was injected intramuscularly to change the fever to a tertian rhythm (Whelen and Shute 1943). After eleven days' fever mepacrine was administered and the malaria was rapidly controlled.

Follow-up.—The patient has now been followed for three years since this remission. She has continued well and developed normally. A malarial relapse occurred six months after the original infection; this responded normally to mepacrine. At present she is in good health, with normal blood-pressure and blood chemistry (plasma-proteins, plasma-cholesterol, and blood-urea). Her urine contains a moderate amount of albumin, but no red cells or casts.

Case 2.—A boy, aged 12 years, developed generalised œdema in September, 1950. There had been no preceding sore throat or other infection. At the age of 5 years he had been thought to have a mild form of cœliac disease, but had thrived subsequently.

On examination two weeks after the onset of the œdema, this was found to be generalised, with severe ascites and bilateral hydrothorax. The boy's blood-pressure was 110/70 mm. Hg, and his retinal vessels were normal. His urine contained very much albumin, with a few red cells and hyaline and granular casts. His plasma-albumin level was 0·8 per 100 ml., plasma-globulin level 1·2 g. per 100 ml., plasma-cholesterol level 300 mg. per 100 ml., and blood-urea level 20 mg. per 100 ml.

Progress.—During the next five months the patient's condition remained the same, with minor fluctuations in the œdema; ascites was always prominent and required tapping on seven occasions, when fluid in amounts up to 6 litres was removed. The loss of protein in the urine averaged 10 g. daily. The following treatments were successively tried during this period: (1) dextran in saline solution, 1 litre infused intravenously; (2) mercurial diuretic (mersalyl) 0·5, 0·5, and 1·0 ml. intravenously at three-day intervals for three doses; (3) A.C.T.H. 80 mg. intramuscularly in divided doses daily for eleven days; and (4) large doses of citrate—sodium citrate 240 g., potassium citrate 60 g., citric acid 300 g.—for four days, followed by half these quantities for a further twenty-one days. On Nov. 9, 1950, the patient

seen in a fourth child with a nephrotic syndrome due to a type-I nephritis.

Malarial mosquitoes were provided by the malaria reference laboratory, Horton Hospital, Epsom. I am most grateful to Sir Gordon Covell, director, and Mr. P. G. Shute, assistant director, for their collaboration.

REFERENCES

Barnett, H. L., McNamara, H., McCrory, W., Forman, C., Rapoport, M., Michio, A., Barbero, G. (1950) *Amer. J. Dis. Child.* 80, 519.
Ellis, A. (1942) *Lancet*, i, 1.
Rapoport, M., McCrory, W. W., Barbero, G., Barnett, H. L., Forman, C. W., McNamara, H. (1951) *J. Amer. med. Ass.* 147, 1101.
Riley C. M. (1950) *Amer. J. Dis. Child.* 80, 520.
Whelen, M., Shute, P. G. (1943) *J. trop. Med. Hyg.* 46, 1.

MALARIAL THERAPY IN LIPOID NEPHROSIS

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IN lipoid nephrosis the response to routine methods of treatment has always been disappointing. Dietary modifications, with salt restriction and increased protein intake, do not produce spectacular results; and the benefit often noted from the use of diuretics is almost always followed by recurrence of the pre-existing œdema. The effect of adrenocorticotropic hormone has likewise been disappointing. Riley (1951) reports that in 9 out of 14 cases treated with A.C.T.H. diuresis was produced, but in only 5 did this diuresis lead to complete clearance of their œdema, and 4 of these relapsed shortly afterwards. In only 1 of the relapsed cases did a further course of A.C.T.H. have any beneficial effect.

In the past it has been noted that some nephrosis patients have had a considerable diuresis, followed by a long remission or permanent cure, immediately after recovery from an acute febrile infection. Applying Hans Selye's concept, I felt that this effect might be due to stimulation of the active defence phase of the adaptation syndrome. If this was so, it seemed that the artificial induction of some non-hazardous disease which could be readily controlled might lead to remission or even cure. I therefore decided to use malaria in a case of lipoid nephrosis which had not responded to other treatment, and was gradually becoming completely waterlogged. Malarial therapy has been used in this case on two occasions separated by an interval of two years, and in both instances the results have been rapid and spectacular.

CASE-RECORD

A boy, aged 2 years and 2 months, was admitted to hospital on July 1, 1949, with a history of an acute onset of scrotal œdema three days previously, followed by enlargement of the abdomen and, within forty-eight hours, massive albuminuria. He had œdema of the legs and scrotum, a large collection of ascitic fluid in his abdomen, and puffiness of his face. His urine was sterile and contained a very heavy deposit of albumin; no pus, blood, or casts were found. The blood-urea was 28 mg., the blood-cholesterol 380 mg., and the serum-protein level 3·5 g., per 100 ml.

Treatment and Progress.—He was given a high-protein salt-free diet, and various forms of treatment were adopted during the next few weeks to evoke effective diuresis. He did not respond to 'Diuretin,' a 500 ml. transfusion of plasma had no obvious effect, and, though there was a good initial response to mersalyl, the œdema quickly recurred. During this time a brief pyrexia was produced on one occasion by an injection of T.A.B. vaccine 0·25 ml. but did not provoke diuresis. At the end of five weeks the œdema had greatly increased, and the boy was becoming waterlogged.

Induction of Malaria.—On Aug. 4, 1949, 5 ml. of malarial blood was injected intramuscularly, and on Aug. 15, the malarial attack began with a mild rigor (104°F). The temperature curve thereafter was of classical periodicity. The boy was allowed six pyrexial peaks (only one further mild rigor occurred), and on Aug. 25, to end the attack, a combined course was started of proguanil 50 mg. t.i.d. for twelve days, and mepacrine 50 mg. t.i.d. for the first forty-eight hours, and thereafter once daily for the next three weeks.

Remission.—Diuresis began two days after the end of the attack of malaria and was copious for the next six days, at the end of which the boy was free from œdema. His weight, which before the onset of diuresis had been 37 lb., was now 30 lb.; his serum-protein level rose during the next ten days to 5 g. per 100 ml., and blood-cholesterol level fell to 271 mg. His urine still showed a cloud of albumin. On Sept. 8, 1949, he was discharged from hospital, and thereafter he attended the outpatients department at three-month intervals until he relapsed almost exactly two years later—on July 6, 1951—when he was readmitted to hospital. During this two-year interval his urine always showed a cloud of albumin, but he remained almost free from œdema, except once or twice when, after coryza, his face was "puffed up" for about a week. No definite cause could be found for the recurrence of his generalised œdema, which was as rapid in its onset on the second occasion as it had been in the previous attack.

On readmission his blood-urea was 30 mg., the serum-proteins 3·8 g., and the blood-cholesterol 583 mg., per 100 ml. His urine contained a very heavy deposit of albumin but was free from pus, blood, and casts.

Treatment with Dextran.—On July 9 and 16, 1951, dextran 500 ml. was given intravenously. It did not produce any diuresis, and the boy became waterlogged (fig. 1).

Induction of Malaria.—He was then inoculated with malaria, and his pyrexia began on Aug. 3, 1951. The temperature pattern in this attack was not quite classical, and the infection did not seem to be heavy, parasites being scanty in the blood films; but a satisfactory pyrexia was maintained for nine days, when the attack was terminated as before with a combined course of proguanil and mepacrine. Seven days after the end of the attack a profuse diuresis took place, and within five days he was free from œdema. His weight had fallen from 53 to 43 lb., and his blood-cholesterol was now 390 mg. per 100 ml., with blood-urea 22 mg.

Follow-up.—He was discharged from hospital on Sept. 8, 1951, and has since attended the outpatients department monthly. The slight albuminuria present on discharge from hospital has now disappeared, and he has been free from œdema (fig. 2). On Jan. 11, 1952, his blood-urea was 30 mg. per 100 ml. and his blood-cholesterol 281 mg. His urine was free from albumin and a urea-clearance test showed 165% average normal function.

The disappearance of protein from the urine and a highly satisfactory renal function test suggest that the present remission may prove to be permanent.

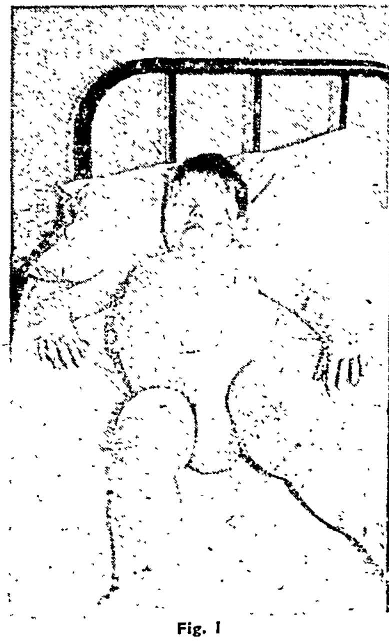

Fig. 1

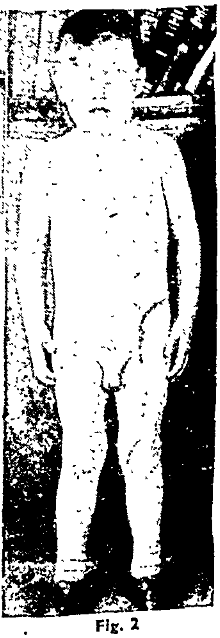

Fig. 2

Fig. 1—Lipoid nephrosis before second induction of malaria.

Fig. 2—Same patient as in fig. 1 after malaria therapy of lipoid nephrosis.

DISCUSSION

Lipoid nephrosis falls naturally into the category of Selye's diseases of adaptation. It is capable of spontaneous and permanent remission; it responds, even though transiently, to A.C.T.H.; and remission or recovery has often followed an acute febrile infection.

The disease is a general one, and affects tissues other than the kidney. It is of particular interest that the œdema has been observed to precede the albuminuria by several days (Marriott 1949). The renal disorder itself is functional and selective; it is accompanied by a disturbance of cholesterol metabolism and by widespread disturbance of electrolyte concentrations in the blood and tissues (Fox and Slobody 1951).

In the nervous control of the adaptation syndrome the hypothalamus is the principal seat of coördination of the general defence mechanisms. It stimulates to activity both the nervous system and the anterior lobe of the pituitary gland, and is itself influenced, as regards the extent of its activity, by the prefrontal regions. The prefrontal area and the hypothalamus together may be regarded as an interdependent and "resonating" mechanism, and in the chain of events which constitute the general adaptation syndrome any disorder of function occurring in this system might well distort its basic pattern, particularly in its early stages when changes in electrolyte concentrations are taking place. Recent work suggests that the frontal lobes contain a mechanism involved in the regulation of electrolyte concentrations in the body-fluids; and considerable disturbance of renal function, and changes in the normal electrolyte pattern in the blood, follow stimulation of, or injury to, the posterior portions of the orbital areas (Cort 1948, McLardy 1950, Sweet et al. 1948). The transient response to A.C.T.H. compared with the prolonged and commonly permanent remissions following varying types of infection, suggests that it requires the production of the whole chain of events which makes up the general adaptation syndrome to effect a successful prolonged or permanent response.

It is not surprising that a disorder like lipoid nephrosis should predominate in infancy and early childhood, when full functional maturity of the resonating mechanism mentioned above has not yet been achieved. The disturbance of cholesterol metabolism is not easy to explain, for detailed knowledge of the mechanism through which this function is mediated is still very scanty. A similar type of disorder has been found after experimental injury to hypothalamic structures (Gildea and Man 1940); but it is not yet possible to advance any acceptable theory about the reason for its occurrence in the course of lipoid nephrosis.

In brief, lipoid nephrosis in infancy and early childhood seems to be brought about by a functional disturbance occurring, in certain susceptible persons, in the course of responses of the central nervous system to some types of stress which cannot be clearly identified but probably vary from case to case.

CONCLUSION

A case is described in which malarial therapy apparently cured lipoid nephrosis in a boy aged 5 years.

The nature of the syndrome is discussed, and an explanation of its causation is put forward.

It is suggested that malarial therapy may prove of value in other diseases of adaptation which occur during infancy and childhood.

I am indebted to Mr. P. G. Shute, of the Malaria Reference Laboratory, Horton Hospital, Epsom, for the infected mosquitoes. The species of parasite was *Plasmodium vivax* (benign tertian), Madagascar strain, and it was transmitted by *Anopheles atroparvus*.

References at foot of next column

MANAGEMENT OF RESPIRATORY INFECTIONS IN PATIENTS SEVERELY PARALYSED BY POLIOMYELITIS

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PATIENTS with a severe degree of residual paralysis of the respiratory muscles after anterior poliomyelitis present a considerable problem during the winter months. This applies particularly to those with a vital capacity of less than 1000 c.cm. The most minor infection of the upper respiratory tract may in a short time involve the bronchi, and, because the patients cannot cough up the mucous secretions, segmental, lobar, or whole-lung collapse may follow.

The problem is a comparatively simple one: to tide the patient over the period of infection and during that time to keep the bronchial tree as free as possible of the mucus which tends to accumulate there.

A sore throat or cold may in these patients, after 2 or 3 days of minimal symptoms, suddenly produce a gross catarrhal bronchitis. If it is left until this stage the physician may be called upon to deal with a sudden bronchial blockage. In these circumstances it has been the practice at the Royal National Orthopædic Hospital, Stanmore, to ask the physiotherapists to try to clear the bronchial obstruction and re-expand the collapsed area of lung. Frequently this has been impossible, and bronchoscopy has been necessary. Bronchoscopy in any patient is unpleasant and for these particular patients thereafter every cold is a terrifying experience.

The physiotherapists were handicapped by having no means of knowing just what was happening in the patient's chest. Moreover, on finishing a treatment they could not know whether their efforts had been useful or not. The method of clapping the uppermost side of the chest with the cupped hand as a means of dislodging mucus rapidly became painful to these thin patients and this made it difficult to continue treatment for as long as was necessary. A new routine was therefore devised, and this has been in use for the last two winters.

ROUTINE

(1) All severely paralysed cases have a radiograph of the chest taken on admission, with the inspiratory and expiratory positions on the same film. The diaphragmatic movements are therefore known. The vital capacity is also determined with a gasometer-spirometer and this measurement is repeated about every 6 weeks.

(2) All cases of even the slightest throat or nose infection in patients with residual paralysis of the chest are notified to the physician immediately they occur.

(3) Chemotherapy is immediately started—e.g., 'Estopen' 500,000 units 8-hourly.

(4) Cultures from the throat and/or nose are taken to determine sensitivity of organisms, so that, within 48 hours, alternative chemotherapy may be given if necessary.

(5) The physiotherapists have been taught how to examine the chest by inspection, by estimation of

DR. BYRNE: REFERENCES

Cort, J. H. (1948) Cited by Livingstone, R. B., Fulton, J. F., Dulgade, J. M. R., Sachs, E., Brandler, S. J., Davies, G. D., *Res. Publ. Ass. nerv. ment. Dis.* 27, 405.
Fox, C. L. jun., Slobody, L. B. (1951) *Pediatrics*, 7, 186.
Gildea, E. F., Man, E. B. (1940) *Res. Publ. Ass. nerv. ment. Dis.* 20, 501.
McLardy, T. (1950) *J. Neurol., Neurosurg., Psychiat.* 13, 106
Riley, C. M. (1951) *Pediatrics*, 7, 457.
Marriott, H. L. (1949) Cited by Spence, J. C., Davidson, G. *In* Paterson, D., Moncrieff, A., Garrod, Batten and Thursfield's Diseases of Children. London; vol. II, p. 440.
Sweet, W. H., Cotzias, G. C., Seed, J., Yakovlev, P. I. (1948) *Res. Publ. Ass. nerv. ment. Dis.* 27, 795.

expansion of both sides with the hands, by percussion, and by auscultation. They are able to find out for themselves whether they are dealing simply with a sticky chest in which air entry and movement is equal on the two sides, or whether there is any area of the chest more particularly full of mucus than any other, or finally, and most important, whether there is any particular area of the chest in which movement or air entry are deficient. This instruction of the physiotherapist and the constant coöperation between her and the physician is of the utmost importance. Really effective physiotherapy cannot be maintained for these patients unless the physiotherapist knows what she is trying to do, and also, when she leaves the bedside, knows whether she has done it. The girls working in the department are taught how to recognise the existence of accumulations of mucus in the tubes, consolidation, bronchial obstruction, and pulmonary collapse. They are also taught the anatomical arrangement of the main bronchi so that if, for example, a right lower lobe has collapsed, they know the best posture in which to place the patient during their efforts to clear the affected area.

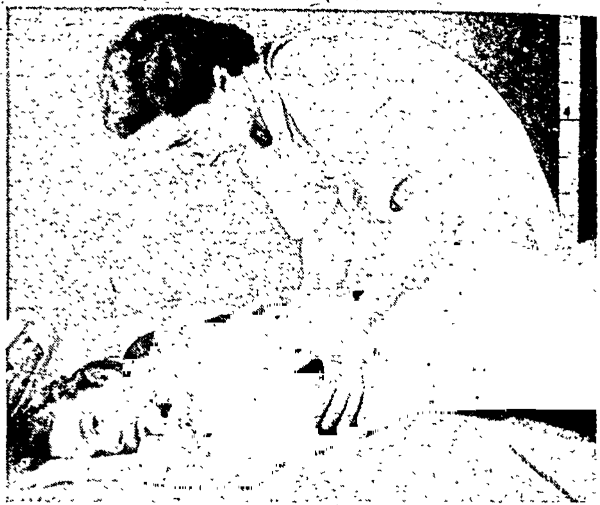
(6) The patients, if old enough, are told of the dangers of respiratory infection. It is made clear to them that *they should complain at once if they feel a cold or a sore* throat coming on, or if they suddenly have increased difficulty in breathing. This understanding of the situation by the patients and their coöperation are important. Preventive measures can be taken at the first opportunity and the patients themselves feel that the situation is under control; their anxiety is lessened and their confidence in those treating them is increased.

MANAGEMENT OF CATARRHAL BRONCHITIS

There are three stages in this emergency: (1) excess mucus generally in the bronchial tree; (2) blockage of a bronchus by mucus; and (3) collapse of lung beyond a blockage. Most of the patients are in stage 1. Some will progress to stage 2. It is looked upon as a failure if any reach stage 3.

During such an infection it may have to be accepted that a particular patient's bronchi will be more or less clogged with mucus for anything from 7 to 20 days. During this time it is the duty of the physiotherapist to attend to the patient four or more times a day to keep the bronchi reasonably free. There is one quite obvious method of doing this—coughing. As the patient cannot do this adequately for himself, the ideal treatment is to produce a reasonable cough for him. But since such treatment may have to continue for 2 or 3 weeks, it must not produce soreness of the chest wall. The most effective and least trying method of producing a cough is simply for the physiotherapist to place one hand on the front of the chest and one on the back and to press the two together in unison with the patient's feeble cough. The patient lies on one side with the uppermost knee flexed to prevent rolling into the prone position. The physiotherapist stands behind the patient with one hand on the front of the chest and the other on the back. The hand in front presses backwards and slightly downwards. The hand behind simply exerts counter-pressure (see figure). Mucus can be coughed up in this way by patients with vital capacities as low as 300 c.cm. Gravity will also help; but we are dealing with sticky mucus and it is no good expecting gravity and assisted coughing to clear a particular set of bronchial tubes in a minute or two.

The technique of clapping with the cupped hands and vibrations, which has been found valuable in cases with postoperative pulmonary collapse, has for two reasons been found unsuitable in paralysed patients. Firstly, the ordinary patient can be made to cough by these methods whereas the paralysed patient has to be helped to produce the cough, which his weak chest muscles cannot do for him. Secondly, the method rapidly becomes too *painful to be borne.*



Physiotherapist assisting patient to cough.

Generally Sticky Chest.—In clearing the lung as much as possible, the physiotherapist starts with the most vulnerable part—i.e., the lower lobes. The patient is placed on one side with the foot of the bed blocked to 20°. A greater tilt produces uncomfortable congestion of the face and the weight of the abdominal viscera against a weak diaphragm may further decrease the vital capacity. Four or five assisted coughs are followed by a pause of 10–20 seconds and then four or five more coughs. This sequence is continued for some 10–15 minutes. After it has been ascertained with the stethoscope that the first side is reasonably clear of rhonchi, the patient is turned on the other side and the procedure repeated. If necessary the patient can then be placed in the semi-supine position. The physiotherapist places one hand over the scapula behind and the other over the upper zone on one side in front. Coughing is assisted until first one upper lobe and then the other are reasonably clear. This procedure is repeated three or four times a day.

There is one addition to this routine which has been found of value. Mucus collects most dangerously during the night. The patient will probably wake up in the ward about 6 A.M. and the physiotherapist will not come on duty until after 9 A.M. It is both dangerous and unnecessary to leave the patient with a very sticky chest for those 3 hours. All that is needed is to block the bed to 20° and place the patient prone and head down with a Bragg-Paul respirator round the chest. He can then cough in bouts in unison with the expansions of the pneumatic jacket. In 20–30 min. a patient with a sticky chest will often have coughed up a large quantity of mucus and the chest be reasonably clear.

Bronchial Blockage.—Most patients will know when a sudden bronchial blockage has occurred. They are aware of increased difficulty in breathing. The area involved will move poorly, breath sounds will be absent, but it will still be resonant. It is the air in the lung beyond the block which enables assisted coughing at this stage to dislodge the mucus so much more easily. The patient is laid in a position with the blocked bronchus uppermost, and the treatment started. In a short time it may be found that the block has been cleared and air entry restored. But it does depend upon dealing with the emergency as quickly as possible.

A girl, aged 18, suddenly became conscious of increased difficulty in breathing. She was seen within 20 min. and it was found that though the right chest was resonant, there were no inspiratory breath sounds. Assisted coughing while lying on her left side cleared the block in less than 2 min. and breath sounds were again heard normally.

Pulmonary Collapse.—When the air beyond the block has been absorbed, there will be dullness, poor movement, and either no air entry or distant bronchial breathing. Assisted coughing may again clear the blockage and avoid bronchoscopy.

A small boy (not a poliomyelitis patient) had a generalised postoperative bronchitis with complete collapse of the middle lobe. A further X-ray film, taken after 10 min. of assisted coughing, showed that the lobe had half re-expanded. Hourly treatments followed. Next morning the middle lobe was almost normal and full re-expansion was obtained. Pulmonary collapse in poliomyelitis cases has been treated with similar success.

Finally, if segmental, lobar, or complete pulmonary collapse has occurred and physiotherapy has failed, bronchoscopy must be performed. We are fortunate to have the coöperation of Mr. A. M. Zamora, the ear, nose, and throat surgeon to the hospital. He has bronchoscoped such patients for us under local or, in younger patients, general anæsthesia. The general anæsthetic is usually thiopentone sodium, but it is sometimes necessary to keep a Bragg-Paul respirator running and to pass oxygen down the side tube of the bronchoscope. Mr. Zamora uses fine catheters attached to the electric suction apparatus to clear the bronchi, and he has usually obtained re-expansion. I am sure, however, that he will not mind my saying that we now think that we have failed if we have to ask for his help.

The same routine can usually be followed in iron-lung patients by sliding the tray of the tank out and tilting downwards. If necessary oxygen can be given by nasal catheters during treatment. Treatment in the tank is not at all easy. Some patients who are just able to breathe when out of the tank if they are well, may of course need to return to respirator life when their vital capacity is reduced by the infection.

I must acknowledge the help that the scheme has received from the staff of the physiotherapy department at Stanmore. Its success would have been impossible without their enthusiastic coöperation.

CORTISONE AND A.C.T.H. IN EXOPHTHALMIC OPHTHALMOPLEGIA

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EXOPHTHALMIC ophthalmoplegia is a relatively rare condition in which increase in bulk of the orbital contents leads to their protrusion and is associated with disorder of function of some or all of the extrinsic ocular muscles. Its causation is complex and ill understood, obscurity persisting despite much experiment.

The classical signs of thyrotoxicosis include lid retraction, which results in widening of the palpebral aperture and explains the staring look of the thyrotoxic. In such patients an abnormal extent of the globe's surface is exposed, and the illusion of proptosis is created where, in general, none exists. As Ida Mann (1946) points out, such an effect can be produced in many animals by agents which stimulate smooth muscle.

Marine et al. (1933) showed that exophthalmos so produced was presumably accomplished through a nervous mechanism, since it could be abolished by removal of the superior cervical ganglion, and it seems possible that the sympathetic stimulants which produce this effect act more readily in the presence of excess thyroxine.

Mulvany (1944) attributed the exophthalmos of thyrotoxic patients to a spastic contraction of the orbital smooth muscle secondary to increased sympathetic stimulation.

Pochin (1939) observed the effects of electrical stimulation of the cervical sympathetic in three patients during the operation of cervical sympathectomy. Retraction of the upper and lower lids and pupillary dilatation developed, but in no case did exophthalmos result.

That exophthalmos in man is not to be explained on the basis of increased sympathetic activity has been shown by Russell Brain (1939), who reported its development in a patient with paralysis of the cervical sympathetic from an existing syringomyelia.

The experimental production of exophthalmos has been largely concerned with the use of extracts of the anterior pituitary gland.

Marine and Rosen (1933) and Smelser (1936) produced exophthalmos in guineapigs by injecting extracts of the anterior lobe of the ox pituitary; these results were even more readily obtained when thyroidectomy had been performed before the injections. Smelser (1939, 1943) further demonstrated that such injections in thyroidectomised guineapigs caused exophthalmos and swelling of the orbital fat, which was almost entirely the result of an increase in the water content of this tissue. He showed that this process of connective-tissue hyperplasia and œdema was not confined to the orbital fat but also involved other body fats, though to a lesser extent. The extrinsic ocular muscles share in this pathological change, and Mulvany (1944) ascribes the ophthalmoplegia to a myopathic condition dependent on œdema, round-cell infiltration, and fibrosis.

The substance in anterior-pituitary extract responsible for these effects has not been definitely identified, but most published observations accept a close relation between the exophthalmic principle and the thyroid-stimulating hormone of the anterior pituitary (T.S.H.). Dobyns (1946) gave injections of anterior-pituitary extract containing a fairly high amount of thyrotropic hormone to guineapigs and demonstrated a correlation between the production of exophthalmos and mobilisation of fat from the depots associated with fatty changes in the tissues. However, the work of Jefferies (1949) suggested that experimentally induced exophthalmos cannot be attributed to thyrotropic activity alone, nor to pituitary-induced mobilisation of fat, and in the human disease Falconer and Alexander (1951) were unable to show a constant relation between the development of exophthalmos and the levels of circulating T.S.H.

Inhibition of T.S.H. secretion and thyroid function has been known to follow a continued dose of cortisone or of adrenocorticotropic hormone (A.C.T.H.) and is probably mediated through the pituitary, since it can be overcome by the giving of thyrotropic hormone (Hill et al. 1950). On these grounds it seemed that a trial of cortisone and A.C.T.H. in exophthalmic ophthalmoplegia would be justified. This present report is concerned with the effect of these drugs in five patients with this condition. We have previously had experience of the known ability of these substances to promote saline diuresis in certain œdematous states, and bearing in mind the belief that œdema of the orbital tissues plays a part, at least, in the production of exophthalmos we decided to investigate the sodium balance of these patients undergoing this form of treatment.

PROCEDURE

All the patients, except case 1, were given a diet providing a calculated daily sodium intake of 800 mg., together with a constant fluid intake. The urine was collected in 24-hour samples, and the sodium content was estimated. Measurements of proptosis were undertaken weekly with the Hertel exophthalmometer, the same person being responsible for all readings. The normal reading was taken as 17 mm. on the scale, and the results were expressed as millimetres of protrusion beyond this base-line. The clinical appraisal of thyroid function was supplemented by routine tests of basal metabolic rate (B.M.R.) and blood-cholesterol levels. Of the five patients three were male and two female (which emphasises the difference in sex-incidence compared with thyrotoxicosis). The youngest was aged 49 and the eldest 79.

CASE-RECORDS

Case 1.—A male postal inspector, aged 55, had proptosis and diplopia which had antedated by a few months the clinical recognition of thyrotoxicosis in 1945. The thyrotoxicosis had been controlled with thiouracil, but proptosis had gradually increased, with ocular paralysis and diplopia

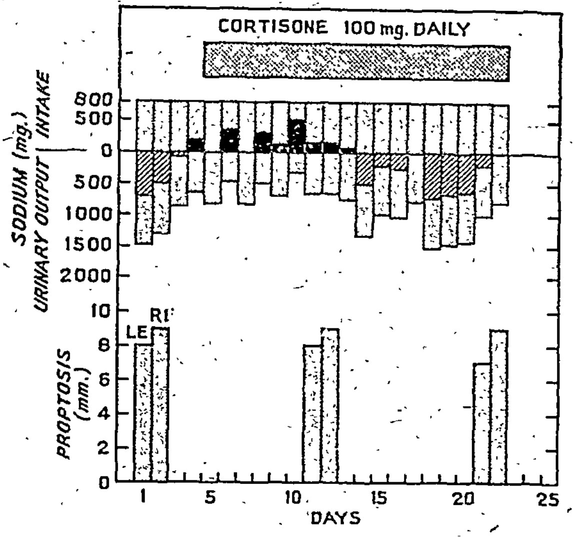

Fig. 1—Sodium balance in case 2: black areas, positive sodium balance; hatched areas, negative sodium balance; proptosis is expressed as mm. of protrusion beyond base-line of 17 mm. on Hertel exophthalmometer scale.

prominent in all directions of gaze. Thiouracil was discontinued in 1948, and he then remained well but without further change in the eye signs until May, 1951, when a further phase of thyrotoxic activity developed.

On admission to hospital in June, 1951, he was severely thyrotoxic (B.M.R. + 54%) and had the eye signs of exophthalmic ophthalmoplegia. There was 10 mm. of proptosis in the left eye and 6 mm. in the right, associated with paralysis of the external recti, superior recti, and inferior oblique muscles of both eyes.

Treatment.—Thiouracil therapy was recommenced, but after 3 weeks' treatment, and with the patient still obviously thyrotoxic, agranulocytosis supervened, and thiouracil was discontinued. At this time the white-cell count had fallen to 1200 per c.mm. (polymorphs 4%) the sternal marrow showing marked hypoplasia of both the erythroid and myeloid elements. Treatment with penicillin 250,000 units 6-hourly and A.C.T.H. 25 mg. 6-hourly was instituted, and there followed a rapid improvement in the clinical and hæmatological picture. A.C.T.H. was continued for 15 days, and coincidentally with its administration a notable lessening of proptosis was observed and confirmed by measurement.

Progress.—2 weeks after treatment the estimations showed only 5 mm. of protrusion in both eyes. The range of ocular movement increased, particularly as regards the external recti and inferior oblique muscles. The thyrotoxic element was also rapidly controlled, and the normal thyroid status following A.C.T.H. therapy was in notable contrast with the conspicuous, almost florid, thyrotoxicosis before treatment. The B.M.R. 2 weeks after A.C.T.H. had been discontinued was +9%, when he was discharged home.

Follow-up.—This patient's progress has been followed for 3 months. He has maintained his improvement and is well and back at work. There is no evidence of thyrotoxicosis clinically, and there has been no increase in exophthalmos.

In this case both the proptosis and ophthalmoplegia were favourably influenced by a 15-day course of A.C.T.H. Coexisting thyrotoxicosis was effectively and rapidly controlled. Sodium-balance estimations were not made.

Case 2.—A man, aged 49, developed thyrotoxicosis in 1945, when his eyes became prominent. After thyroidectomy proptosis increased and a mild subthyroid state required thyroid therapy.

On admission in August, 1951, he presented the eye signs of exophthalmic ophthalmoplegia. There was 8 mm. of proptosis in the left eye and 9 mm. in the right, with weakness of the external recti most marked in the right eye. Convergence was poor. There was no evidence of myxœdema clinically, and his general condition was good. Psychologically his mood was one of mild depression; he remained socially withdrawn and completely lacking in spontaneity. The B.M.R. was −12% and the blood-cholesterol level 270 mg. per 100 ml.

Treatment.—Thyroid medication was discontinued on admission. Dietary regulation of sodium and fluid intake was undertaken, and after a preliminary control period cortisone therapy was begun at a dosage of 100 mg. daily and continued for 17 days.

Progress.—No significant change in the exophthalmos was observed, but convergence improved. The urinary excretion of sodium was somewhat variable, showing a tendency to a negative balance during the latter half of therapy (fig. 1). No change was noted clinically in thyroid status, though the B.M.R. fell to − 26%. The blood-cholesterol level fell slightly to 240 mg. per 100 ml. after treatment.

This patient with post-thyroidectomy myxœdema and exophthalmic ophthalmoplegia did not respond to a 17-day course of cortisone. We hope to use A.C.T.H. later.

Case 3.—A housewife, aged 63, had developed proptosis and diplopia in 1944. A course of stilbœstrol had no effect on the eyes and was discontinued after 3 months, because of uterine bleeding. By the next year thyrotoxicosis was evident clinically, and treatment with thiouracil was begun. Control of the thyrotoxicosis was never entirely satisfactory, being attended by frequent drug reactions; and, after a thyroid crisis had been successfully treated in 1949, the patient underwent thyroidectomy. There was a postoperative increase in the proptosis, the eyes feeling uncomfortably full, with both horizontal and vertical diplopia. The subsequent development of myxœdema necessitated thyroid medication.

On admission the patient was a plump pleasant woman, still evidently slightly hypothyroid, judged by her facies, skin, and hair. Her B.M.R. was −2% and blood-cholesterol level 150 mg. per 100 ml. There was 7 mm. of proptosis in the left eye and 8 mm. in the right, with bulging of the supratarsal parts of both upper lids and fullness of the lower lids. Upward movement was defective in both eyes, weakness of the left superior rectus being most evident. Lateral movement was less severely restricted.

Treatment.—The usual dietary régime was adopted, and after a preliminary control period cortisone therapy was commenced at a dosage of 100 mg. a day and continued for 24 days. Thyroid extract was stopped on admission.

Progress.—Regression of proptosis and improvement in ocular muscle weakness were greatest at the end of the 3rd week of treatment, and were associated with gradual but increasing hypothyroidism, the patient complaining of the cold in somewhat huskier tones. The B.M.R. on cessation of cortisone was −28% and blood-cholesterol level 180 mg. per 100 ml., when thyroid therapy was started again. After

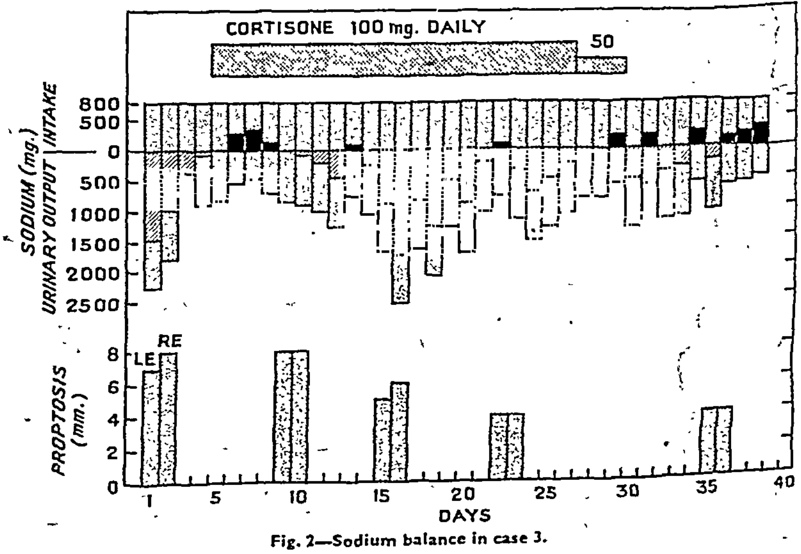

Fig. 2—Sodium balance in case 3.

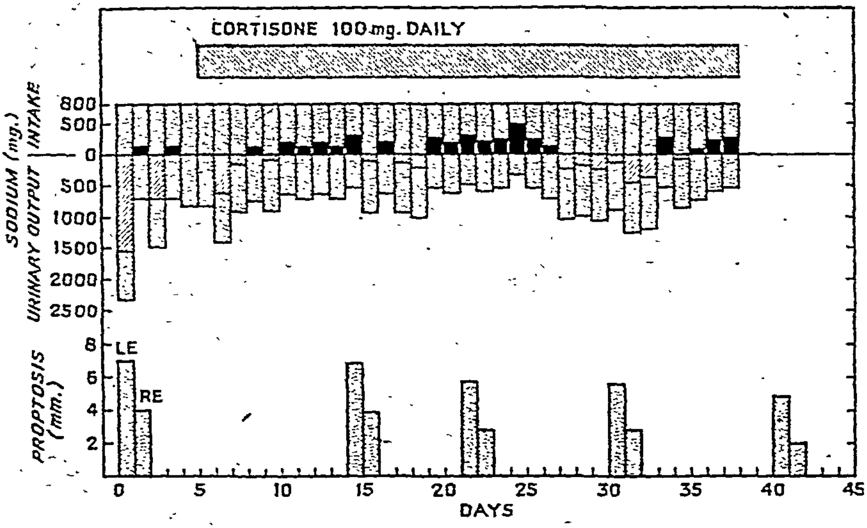

Fig. 3—Sodium balance in case 4.

an initial 3-day phase of slight sodium retention, a saline diuresis developed towards the end of the 2nd week of cortisone administration, the bulk of the sodium loss preceding the period of greatest ocular recession (fig. 2).

Follow-up.—When she was seen again 2 months after her discharge from hospital there had been some increase in proptosis.

This patient with post-thyroidectomy myxœdema and exophthalmic ophthalmoplegia showed a significant response to cortisone, with later partial relapse after treatment had been discontinued. The improvement in the local condition of the eyes was associated with increasing hypothyroidism, and could perhaps be related to the establishment of a negative sodium balance.

Case 4.—A man, aged 79, had had exophthalmic ophthalmoplegia diagnosed in 1950, when left-sided tarsorrhaphy was undertaken. He was otherwise well and active, without clinical evidence of thyroid dysfunction.

On admission in August, 1951, abnormal signs were confined to the eyes, the left eye showing well-marked œdema and 7 mm. of proptosis, with conjunctival injection and a mild blepharitis. The right eye was less severely affected, with 4 mm. of proptosis. Weakness of the ocular muscles was most evident for upward movement of both eyes, lateral movement being only slightly impaired. The B.M.R. was −18% and the blood-cholesterol level 120 mg. per 100 ml.

Treatment.—After a preliminary 6-day period of controlled sodium and fluid intake, cortisone was started at a dosage of 100 mg. daily and continued to a total of 3·3 g. in 5 weeks.

Progress.—Proptosis regressed significantly, but not dramatically, the patient remarking on the new-found sense of comfort in the eyes. Measurements of exophthalmos after cortisone was discontinued showed 5 mm. of protrusion in the left eye and 2 mm. in the right. Increase in the range of ocular movement was greatest in the inferior oblique and superior rectus muscles of both eyes. No significant change took place in the pattern of urinary sodium excretion (fig. 3). No alteration in thyroid status was clinically appreciable, and the B.M.R. after treatment was still −18%. The blood-cholesterol level was 110 mg. per 100 ml.

This patient showed slight but definite objective improvement in the eye signs and considerable subjective improvement. Sodium balance and thyroid function were unaltered.

Case 5.—A housewife, aged 50, had first noted diplopia and undue prominence of the left eye in December, 1950. She was investigated on this account by the neurological department in May, 1951, when the B.M.R. was normal. She came under our observation a few months later, when she was found to be moderately thyrotoxic (B.M.R. +36%), with the eye signs of exophthalmic ophthalmoplegia, 6 mm. of proptosis being recorded in the left eye and 4 mm. in the right. There was gross weakness of all the ocular muscles, elevation being completely paralysed, lateral deviation severely restricted, and depression least affected.

Treatment.—She was treated with cortisone to a total dose of 2·7 g. in 4 weeks, the salt and fluid intake being controlled and the urinary excretion of sodium estimated as in the previous patients.

Progress.—The most obvious effect of therapy lay in the control of the thyrotoxicosis, the B.M.R. falling to −5%, the patient experiencing a complete remission in this aspect of her illness. The blood-cholesterol level rose from 150 to 260 mg. per 100 ml. Proptosis was uninfluenced, but there was a definite improvement in the range of ocular movement, 20 degrees of elevation being established in both eyes, together with an increase in the horizontal movement. The sodium balance was variable (fig. 4).

The experiment was to have been terminated at this stage of partial recovery, but unfortunately the patient developed a painless abscess at the site of one of her injections. This was incised a week after cortisone had been discontinued, and a general anæsthetic was administered for this purpose without our knowledge. Within a few hours of this procedure the patent complained of severe pain in both eyes, which were found to be rigidly proptosed, inflamed, and œdematous. By the same evening an exposure keratitis was developing in the left eye, where early corneal ulceration was evident the next morning. Tarsorrhaphy was performed on this eye, and treatment with A.C.T.H. was started at a dosage of 25 mg. 6-hourly. Antibiotic cover was afforded by chloramphenicol.

Improvement was extremely rapid and quite outside our previous experience of this malignant condition. Within 3 days the right eye was normal, apart from some 4 mm. of proptosis. By the 6th day the tarsorrhaphy was discontinued, and the left eye could be seen to be well out of danger. 7 days later, measurements of proptosis showed that both eyes were at their preoperative state. When a total of 1·8 g. of A.C.T.H. had been given in 18 days, this drug was "steppage-stopped" and treatment was continued with cortisone 100 mg. daily.

The patient is now attending as an outpatient for her injections of cortisone. The eye signs are much as on admission, but ocular movement has improved. Clinically she is verging on the subthyroid state and shows early "mooning" of the face, though without other evidence of cortisone overdosage.

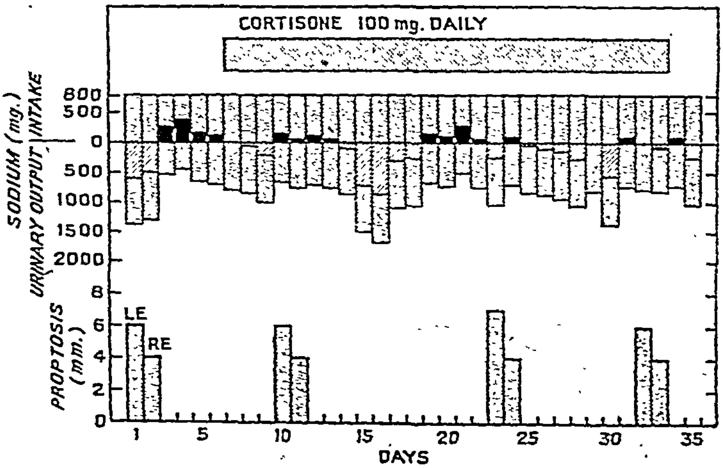

Fig. 4—Sodium balance in case 5.

In this last case the initial treatment with cortisone induced a remission of thyrotoxicosis and some small improvement in the eye signs. The development of malignant exophthalmos following the incision of an abscess under general anæsthesia was of considerable interest, both in the rapidity of its onset and in its satisfactory control with A.C.T.H. It was obviously a grave error to have exposed this patient, whose adrenal cortical function had been depressed by the previous administration of cortisone, to the stress of a general anæsthetic without the further protection of this drug. Probably another factor operating was the loss to the pituitary-thyroid relationship of the balancing action of the thyroid hormone, consequent on the control of the thyrotoxic component. In this case treatment did not significantly change the sodium balance, but these determinations were not continued during the treatment of the dramatic postoperative disturbance with A.C.T.H.

DISCUSSION

Of the five patients treated with cortisone and A.C.T.H. some improvement took place in four. In two (cases 1 and 3) the benefit obtained could fairly be rated as considerable. Case 4 showed a more modest response; and, whereas the original course of cortisone had little effect on the ocular condition of case 5, the rapid control of this patient's post-anæsthetic increase in proptosis was highly encouraging. That the improvement which follows this form of treatment may well be maintained has been shown in one instance by the follow-up of case 1. All the other patients have shown some return to their original state, but in every case some improvement persists to date.

The mechanism of improvement or partial success is far from clear. The results in relation to the balance of body sodium are inconclusive. If relief of the orbital œdema were the responsible factor for the improvement, it might reasonably be expected that only a relatively small loss of body-sodium would effect this change—an amount possibly well within the range of experimental error in a balance determination of this kind. But it is worth recalling that some of the oldest treatments for this condition aimed at securing water depletion by purgation (Means 1948), and possibly the usefulness of thyroid extract lies in its diuretic power rather than in its specific but more speculative property of inhibiting T.S.H. secretion.

The control of thyrotoxicosis was the most notable feature of the treatment of the two patients (cases 1 and 5) in whom this coexisted with exophthalmos and ophthalmoplegia.

The effect of the adrenal steroid hormones in euthyroid persons has been studied by Hill et al. (1950), who report an almost consistent depression of the I^{131} accumulation gradient, and in some a fall in the serum level of protein-bound iodine. They found that the B.M.R. either increased slightly or remained unchanged, a result which can be explained by the known calorigenic effect of cortisone and A.C.T.H., which increase the basal consumption of oxygen in man by a direct action which does not involve alterations in thyroid function (Beierwaltes et al. 1950).

Hill et al. used A.C.T.H. and cortisone in the treatment of six patients with Graves's disease, in three of whom suppression of thyroid function resulted. Their best responses were obtained in those patients who showed the greatest adrenal cortical activity and had the shortest duration of thyrotoxicosis. These same workers used A.C.T.H. in four patients with exophthalmos at a dosage of 40–80 mg. daily. All the patients experienced relief of pain, lacrimation, and chemosis to some extent, and three showed a slight decrease in exophthalmos.

Salassa (1950) treated three patients with severe exophthalmos but without definite evidence of hyperthyroidism, two of whom received cortisone 1 g. in 7 days, and the third A.C.T.H. 1·4 g. in 17 days. There was no significant change in the eye signs in any of the three patients. In these published series, however, the duration of treatment has been short, judged by our experience, and this may have been an important factor bearing on the lack of response.

It has been suggested that two types of thyrotoxicosis exist, the first depending on hypersecretion of T.S.H., and the second a primary thyroid disorder independent of the pituitary factor. It is interesting and possibly significant that in the patients here reported where exophthalmos and thyrotoxicosis were associated (cases 1, 3, and 5) the eye signs of exophthalmic ophthalmoplegia antedated the recognition of thyrotoxicosis by periods varying from a few months to more than a year. In these cases notable improvement resulted from therapy. It would be tempting to build on this somewhat slender evidence the theory that hypersecretion of T.S.H. is the cause of this condition, and that success in treatment follows from its drug-induced inhibition. But the variable results reported by other investigators suggest that malignant exophthalmos is less easily controlled with cortisone and A.C.T.H. than is the simple thyrotoxicosis of Graves's disease. If this becomes common clinical experience, the concept of the primary ætiological rôle of T.S.H. will be less easy to sustain. Perhaps the hyperactive pituitary, believed to be implicated in exophthalmic ophthalmoplegia, is less easily restrained by increased glucocorticoid levels than is the normally functioning gland.

So far as the present study goes, more delicate tests of thyroid function are required to gain further understanding on these points. The B.M.R. is a poor indicator of thyroid function in patients receiving cortisone or A.C.T.H., and in any future work done by us the thyroid uptake and urinary excretion of I^{131} will be used instead. It is also desirable and somewhat more fundamental, if the identity of the exophthalmic principle and T.S.H. is to be accepted or disproved, that the effect of treatment be assessed in relation to any changes in the blood levels of this hormone. This demands a technique of bioassay which we intend to undertake as part of the framework of a further study.

Dobyns (1950) quotes an editorial from a medical journal written some seventeen years ago. This took to task an author who had referred to the problem of the mechanism of exophthalmos as being but little understood. The editorial writer took the firm view that sympathetic overactivity was the causal fault, and expressed the hope for a wider recognition of this fact. Nevertheless in 1952 the problem is still unsolved.

SUMMARY

An attempt has been made to assess the effect of cortisone and A.C.T.H. in exophthalmic ophthalmoplegia.

Five patients were studied. Some improvement in the ocular condition took place in four. Thyrotoxicosis was controlled in the two patients where this coexisted with exophthalmos and ophthalmoplegia.

The results in relation to sodium balance are inconclusive.

Our thanks are due to Mr. H. Moffett, who undertook the sodium estimations, and to Dr. B. Marshall, who was responsible for all the measurements of exophthalmos. We would also like to acknowledge the coöperation received from the Sisters and nurses on the medical wards of the Infirmary and from the patients themselves. We are indebted to the Medical Research Council for the cortisone.

REFERENCES

Beierwaltes, W. H., Wolfson, W. Q., Jones, J. R., Knorpp, C. T., Siemienski, J. S. (1950) *J. Lab. clin. Med.* 36, 799.

Brain, W. R. (1939) *Lancet*, ii, 1217.

Dobyns, B. M. (1946) *Surg. Gynec. Obstet.* 82, 609.

— (1950) *J. clin. Endocrinol.* 10, 1202.

Falconer, M. A., Alexander, W. S. (1951) *Brit. J. Ophthal.* 35, 253.

Hill, S. R. jun., Reiss, R. S., Forsham, P. H., Thorn, G. W. (1950) *J. clin. Endocrinol.* 10, 1375.

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EFFECT OF SPLENECTOMY IN A CASE OF CONGENITAL PORPHYRIA

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CONGENITAL porphyria is a very rare disease which is probably inherited as a mendelian recessive and is characterised by extreme photosensitivity and the excretion of large amounts of uroporphyrin I and coproporphyrin I in the urine and of coproporphyrin I in the fæces. Photosensitivity may occur in other conditions without the excretion of abnormal or excessive porphyrins and also in varieties of porphyria in which smaller quantities of porphyrins are excreted. These have been investigated less completely than classical congenital porphyria, and their relation to this condition remains obscure. The earlier investigations of congenital porphyria were made by Fischer (1915a and b, 1916), by Borst and Königsdorffer (1929), and in this country mainly by Garrod (1923). A new tool for further research into the condition was provided by the discovery of isotopes and by the important discovery of Shemin and Rittenberg (1946) that the nitrogen of glycine was the specific precursor of the nitrogen atoms in the protoporphyrin of circulating hæmoglobin.

Three independent groups of workers (Grinstein et al. 1949, London et al. 1950a, Gray and Neuberger 1950) have fed glycine labelled with N^{15} to patients with congenital porphyria and found high isotope contents in the excreted porphyrins, thus showing that glycine is specifically utilised in the biological synthesis of type-I porphyrins as well as of the type-III porphyrin of hæmoglobin. The labelled porphyrin of the circulating hæmoglobin is greatly diluted with unlabelled material formed before administration of the isotope, but analysis of the data suggests that protoporphyrin, coproporphyrin, and uroporphyrin are derived from a common precursor.

Some differences were found with respect to the changes of isotope content of the hæm of the circulating hæmoglobin with time. The British workers (Gray, Neuberger, and Sneath 1950) performed two separate experiments, in the first of which evidence was obtained suggesting the presence of a proportion of red cells of short life-span. This was in accordance with the relatively low hæmoglobin content and the reticulocytosis. In the second experiment the hæm-isotope curve was almost normal and the slight anæmia had subsided. The New York workers (London et al. 1950a) observed a moderate reticulocytosis associated with a normal hæm isotope curve. On the other hand, the patient studied by the Minneapolis group (Aldrich et al. 1951, Grinstein et al. 1951) had severe hæmolytic anæmia, splenomegaly, reticulocytosis, and greatly increased urobilinogen excretion in the fæces; the isotope results suggest that this patient also had some red cells of very short life-span.

These findings, together with the earlier report on the case Petry (Weiss 1925, Guenther 1925) and those of Mackey and Garrod (1926) on the present case, suggest that the association between congenital porphyria and hæmolytic anæmia is not incidental. Mackey and Garrod suggested that anæmia was not always present, because the increased rate of destruction of red cells was balanced by enhanced erythropoiesis.

Isotope studies have also shown (London et al. 1950b, Gray, Neuberger, and Sneath 1950) that in normal man 20–25% of the fæcal bile pigment is derived otherwise than by the destruction of red cells at the end of their normal life-span of 120–130 days. Thus, if N^{15}-labelled glycine is given to a normal person, the stercobilin is highly labelled during the first few days after isotope feeding as well as when the labelled red cells are being broken down. There is also small but significant labelling between these two periods. A possible source of the bile pigment not derived from circulating mature red cells has been discussed at length (Gray, Neuberger, Sneath 1950), and it appears probable that a substantial proportion is associated with hæmoglobin formation.

We originally suggested that this bile pigment might be derived from the breakdown of hæmoglobin, metabolically labile because of the immaturity of the red cells in bone-marrow, which may be katabolising as well as synthesising hæmoglobin. However, there is an alternative explanation. In the maturing red cells of mammals the rates of porphyrin or hæmatin formation and globin synthesis are on the average fairly well adjusted, and there is no great excess of either. However, some cells may produce a relative excess of hæmatin or of globin. Excess of globin will lead to hydrolysis, and the liberated amino-acids will join the "protein pool," but hæmatin produced in excess will be largely eliminated in the form of bile pigment. This suggestion is supported by the observation that hæmatin is converted into bile pigment (London 1950).

In congenital porphyria about 80% of the bile pigment is derived from the source associated with hæmoglobin formation, and only about 10–20% is derived from red cells at the end of their normal life-span. Since porphyrins of type I do not give rise to stercobilin, it is clear that in congenital porphyria, in addition to the increased formation of uroporphyrin and coproporphyrin, there is a derangement in the formation of the "normal" porphyrin of type III.

No rational treatment of congenital porphyria has so far been possible. The association between anæmia and porphyria discussed above, the general deterioration in our patient's condition, and the report by Watson (1950: see also Aldrich et al. 1951) of the beneficial effect of splenectomy in a possibly atypical case, suggested that our patient might be benefited by the removal of his spleen. We have also investigated the effect of treatment with riboflavine, which according to Stich (1950) decreases the excretion of porphyrin in urine and fæces.

OBSERVATIONS BEFORE AND AFTER SPLENECTOMY

The detailed history of our patient has already been described (Gray and Neuberger 1950, Gray, Neuberger, and Sneath 1950, Gray, Muir, and Neuberger 1950). He was investigated earlier by Mackey and Garrod (1926). Since the first isotope experiments were made, his general condition has deteriorated and he has been found to have low-grade uræmia (blood-urea level 80 mg. per 100 ml.), although the blood-pressure was normal. Albuminuria is now present, but there has been no history suggesting renal disease.

The hæmatological data kindly supplied by Dr. W. M. Davidson are summarised in table I.

The isotope experiment was performed as described in our earlier papers.

Urinary uroporphyrin was determined on twenty-four-hour collections by the method of Sveinsson et al. (1949). "Urobilinogen" in fæces was estimated by the method of Schwartz et al. (1944), which measures all substances soluble in light petroleum and reacting with p-dimethylaminobenzaldehyde under specified conditions and in addition any

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DR. CHANDLER, PROF. HARTFALL: REFERENCES—*continued*

Jefferies, W. M. (1949) *Ibid*, 9, 913.
Mann, I. (1946) *Amer. J. Ophthal.* 29, 654.
Marine, D., Rosen, S. H. (1933) *Proc. Soc. exp. Biol., N.Y.* 30, 901.
— — Cipra, A. (1933) *Ibid*, p. 649.
Means, J. H. (1948) The Thyroid and its Diseases. 2nd ed., Philadelphia, London, and Montreal.
Mulvany, J. H. (1944) *Amer. J. Ophthal.* 27, 693.
Pochin, E. E. (1939) *Clin. Sci.* 4, 79.
Salassa, R. M. (1950) *Proc. Mayo Clin.* 25, 497.
Smelser, G. K. (1936) *Proc. Soc. exp. Biol., N.Y.* 35, 128.
— (1939) *Amer. J. Path.* 15, 341.
— (1943) *Amer. J. Physiol.* 140, 308.

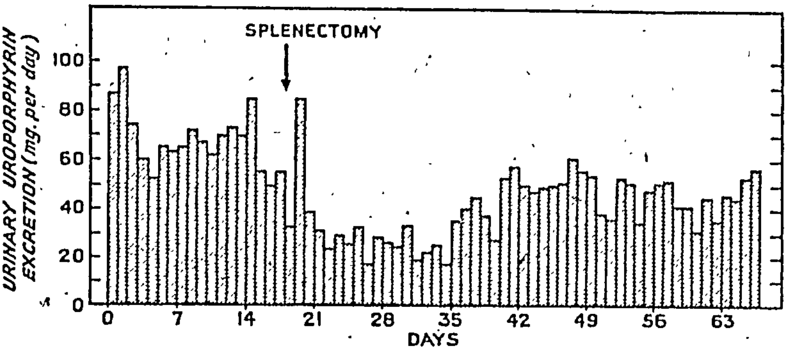


Fig. 1—Urinary uroporphyrin excretion before and after splenectomy

substances which behave similarly after reduction with ferrous ions in an alkaline medium.

The administration of riboflavine had no significant effect on the urinary porphyrin excretion. Previous investigations in this case have shown that injections of ascorbic acid, pyridoxine, 'Plexan,' folic acid, vitamin-B_{12} concentrates, and crude liver extract had no apparent effect on the condition judged by qualitative tests.

Effect of Splenectomy

Urinary porphyrin excretion.—Splenectomy was performed by Mr. H. C. Edwards, on Jan. 19, 1951. Fig. 1 shows the urinary porphyrin excretion before and after the splenectomy. During the first three days after the operation the porphyrin excretion fluctuated considerably owing to variations in urinary volume. The mean preoperative excretion was 73 ± 13 mg. a day. During the following fifteen days the excretion had fallen to an average of 26 ± 6 mg. a day, but during the next thirty-one days this gradually increased, making the mean excretion during this time 47 ± 28 mg. a day. Six months after the operation the average excretion had risen to 61 mg. a day.

It therefore seems that splenectomy led to a temporary diminution in porphyrin excretion, which, however, was not sustained, although the values six months after operation were still somewhat lower than before.

Isotope data.—The patient was given 12 g. of glycine containing 31·6 atom % excess N^{15} in twelve doses $2^1/_2$-hourly, beginning at 6 A.M. on Feb. 5, 1951. Fig. 2 shows the isotope content of the hæm plotted against time. Though the shape of the curve is normal and similar to that obtained in the second isotope experiment described previously, quantitatively the highest isotope content reached is only about half of the corresponding figure obtained when the same quantity of isotopic glycine was fed before operation. There was no evidence of the presence in the circulation of red cells with a very short life-span.

Table II shows the incorporation of N^{15} into the urinary uroporphyrin. A comparison with the figures obtained in the previous experiments shows that no significant change has taken place. The incorporation of the isotope into the fæcal coproporphyrin gave values approximating closely to those obtained in the two earlier experiments done before splenectomy. The stercobilin results, which are also shown in table II, are of particular interest and show clearly that a disturbance of porphyrin metabolism, which is reflected in the high isotope content of stercobilin immediately after labelled glycine feeding, has not been affected by the splenectomy.

Fæcal "urobilinogen" excretion.—Table III shows that the urobilinogen excretion was above the normal range before splenectomy. Immediately after splenectomy there was a definite decrease, which was, however, only temporary, the figures which were obtained five months after splenectomy tending again to be higher.

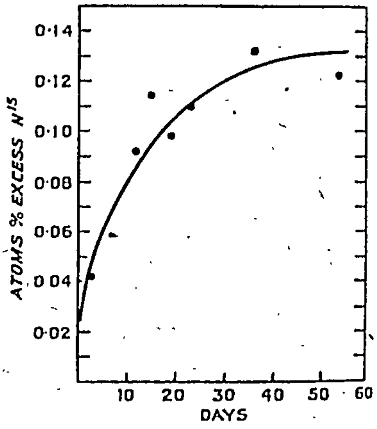


Fig. 2—Incorporation of N^{15} into haem after splenectomy.

DISCUSSION

The results with riboflavine show clearly no noticeable effect on porphyrin excretion in our patient, and are at variance with those of Stich (1950), who claimed that

TABLE I—HÆMATOLOGICAL DATA

Date	Red cells (million per c.mm.)	Hb. (g. per 100 ml.)	Colour-index	Leucocytes (thousand per c.mm.)	Differential count (%)			Remarks
					Poly-morphs	Lympho-cytes	Mono-cytes	
18/2/49	4·6	11·9	1·0	3·1	57	37	6	Packed cell volume 39% ; mean corpuscular volume (M.C.V.) 102 cµ ; mean corpuscular Hb conc. (M.C.H.C.) 32% ; red cells show anisocytosis and poikilocytosis ; 3 nucleated red cells in 100 white cells
3/3/49	4·0	11·9	1·0	4·2	57	33	9	M.C.V. 90 cµ ; M.C.H.C. 33·5% ; reticulocytes 4·8% ; red cells show some anisocytosis and poikilocytosis ; erythrocyte-sedimentation rate (E.S.R.) 11·5 mm. in 1hr. (Wintrobe)
19/5/49	..	12·7	..	3·6	59	31	9	Red cells show anisocytosis and poikilocytosis ; reticulocytes 0·7%
31/10/50	..	12·2	..	5·8	73	16	10	M.C.H.C. 35% ; reticulocytes 4·9% ; E.S.R. 38 mm. in 1 hr. (Wintrobe) ; red cells show little anisocytosis
13/12/50	4·6	11·3	0·8	3·9	61	26	12	M.C.V. 80 cµ ; M.C.H.C. 30% ; reticulocytes 5·8% ; red cells show considerable anisocytosis
19/1/51				Splenectomy				
26/1/51	..	12·2	..	10·5	57	14·5	20·5	Reticulocytes 12% ; red cells show some increase in anisocytosis and very definite punctate basophilia
5/2/51	3·6	11·6	1·08	8·9	47·5	19	22	Red cells show considerable anisocytosis ; definite punctate basophilia accompanied by numerous nuclear fragments ; occasional normoblasts ; platelets increased
12/7/51	4·22	12·2	1·0	10·6	42	30	26	Reticulocytes 12·1% ; normoblasts 9/100 white cells ; moderate anisocytosis ; slight poikilocytosis

this vitamin caused an almost complete and sudden disappearance of porphyrin from the urine of a patient with congenital porphyria. Unfortunately, no clinical data are available concerning his patient(s).

The favourable effect of splenectomy in certain hæmolytic anæmias is well known but not completely understood. In our patient, whose anæmia was not severe, splenectomy was followed by a considerable fall in fæcal "urobilinogen," although there was little change in the hæmatological findings; reticulocytosis in particular was not diminished.

The high isotope content of the fæcal stercobilin also suggests that at least 60% of the total fæcal bile pigment is derived from sources other than the breakdown of the hæmoglobin of red cells which had disintegrated at the end of their normal life-span. Since the total mass of circulating red cells may be presumed to be only slightly lower than normal, and most of the cells had an apparently normal life-span, the amount of bile pigment produced by the katabolism of hæmoglobin of normal cells must have been about 80% of that found in a normal person.

On the other hand, a comparison of the isotope contents of the urinary uroporphyrin with that of fæcal stercobilin suggests that only about 20%, or at the most 40%, of the total stercobilin was derived from this source. It was thus to be expected that the total urobilinogen excretion in the fæces should be at least twice and possibly five times the normal figure. However, the values found immediately after splenectomy are well within the normal limits.

The quantitative interpretation of urobilinogen excretion in terms of hæmatin breakdown is not at all easy. If all the prosthetic group made available by disintegration of hæmoglobin were converted into fæcal urobilinogen the average daily excretion of the latter should be about 300 mg., in view of the fact that the total amount of hæmoglobin in the body of the adult is about 700 g. and the average life-span of the red cell about 125 days. In fact, the values found in normal people are very much smaller, and this point has been commented on by several workers (Watson 1937, Singer 1945, Lemberg and Legge 1949). In the present case isotope contents of stercobilin found before splenectomy suggested increased breakdown of hæmoglobin which had not yet reached the circulation, whereas the urobilinogen excretion was only increased to a moderate extent. It thus seems that the diminished urobilinogen excretion, which was observed immediately after splenectomy, does not necessarily indicate that bile-pigment formation was decreased to any great extent by splenectomy.

TABLE II—ISOTOPE CONTENTS OF URINARY UROPORPHYRIN AND FÆCAL STERCOBILIN FOLLOWING THE ADMINISTRATION OF ISOTOPIC GLYCINE

Glycine (12 g.) containing 31·65 atom % excess N^{15} was fed on days 1–4 in the experiment before splenectomy, but after splenectomy was fed during the first 28 hours of the experiment

Urinary uroporphyrin

Day of experiment	N^{15} content atom % excess	
	Before splenectomy	After splenectomy
1	0·370	0·537
2	1·00	2·106
3	1·50	2·091
4	1·90	1·420
5	1·95	1·041
7	1·26	0·865
8	1·08	—
9–10	0·93	0·601

Fæcal stercobilin

Before splenectomy		After splenectomy	
Days of experiment	N^{15} content atom % excess	Days of experiment	N^{15} content atom % excess
1–4	1·16	2–5	0·476
5–8	1·30	6–9	1·282
9–12	1·36	10–13	0·552

TABLE III—DAILY FÆCAL EXCRETION OF UROBILINOGEN OF PATIENT AT VARIOUS TIMES

Values represent daily averages of 4-day collections.

Date	Fæcal urobilinogen (mg. per day)
Before splenectomy:	
Feb. 15–19, 1949	316
„ 19–23, 1949	226
„ 23–27, 1949	350
Dec. 1–5. 1949	418
„ 9–13, 1949	252
Jan. 19–24, 1950	238
Immediately after splenectomy:	
Feb. 6–9, 1951	87
„ 9–13, 1951	150
„ 15–18, 1951	132
5 months after splenectomy:	
July 10–14, 1951	175
„ 14–17, 1951	341

One further point is worthy of mention: the greatest incorporation of N^{15} into the protoporphyrin of the circulating hæmoglobin was very much higher before splenectomy than was found when similar amounts of isotopic glycine were fed to normal persons or to the patient after splenectomy. It is unlikely that the relatively mild hæmolysis observed in this patient in earlier experiments can account for this phenomenon, and the reason for this high isotope incorporation into hæm and the relative decrease in this last experiment remains obscure.

The reported cases suggest that the fundamental defect in porphyrin synthesis is not affected by the removal of the spleen.

The young girl with congenital porphyria and severe hæmolytic anæmia who was studied by Aldrich et al. (1951) benefited considerably by splenectomy. Anæmia and the sensitivity of the skin to sunlight disappeared, urinary and fæcal porphyrin excretion were greatly reduced, and urobilinogen excretion decreased to normal values. But the metabolic defect consisting of the production of abnormal amounts of coproporphyrin I and uroporphyrin I persisted.

de Marval and Pons (1934) also reported the effects of splenectomy on congenital porphyria. They noted that, though the metabolic defect of porphyria was unchanged, hæmolytic acitivity was greatly reduced, and the sensitivity of the skin to light was decreased.

Aldrich et al. (1951) refer to unpublished observations of Zuelzer and Kaplan on yet another case of congenital porphyria with hæmolytic characteristics. Splenectomy in that patient produced only a temporary improvement in the hæmolytic anæmia, without affecting the underlying porphyria. The skin sensitivity was apparently not altered.

The amount of porphyrin excreted was found to be reduced in the two cases where quantitative measurements were made (in our case this reduction was rather small and temporary); skin sensitivity was not affected in two cases, was improved in one case, and was completely abolished in another case. In our patient, in whom anæmia was slight, hæmatological findings were not affected by splenectomy; in the other cases, where the anæmia was severe, the hæmolytic condition was either improved or abolished. But this remission may only be temporary. It thus seems that splenectomy as palliative treatment may be of value only in congenital porphyria associated with severe hæmolytic anæmia.

SUMMARY

A short review is given of our present knowledge of porphyrin metabolism in congenital porphyria, and evidence showing that the production of large amounts of porphyrins of type I is due to an abnormality in the production of hæmoglobin is summarised.

The association with hæmolysis or hæmolytic anæmia often found in congenital porphyria is thus considered not to be fortuitous.

Splenectomy reduced somewhat the excretion of porphyrin in the urine and of urobilinogen in the fæces, but the hæmatological findings and the sensitivity of the skin to light were not affected by the operation.

We wish to thank Miss M. Pickett and Mrs. B. Higginson for experimental assistance, the Medical Research Council for an expenses grant to C. H. G., the central research fund of the University of London for the purchase of a Spekker absorptiometer, and Dr. R. Bentley and Mr. G. Dickinson for mass spectrometer analyses. We are particularly grateful to Dr. W. M. Davidson, of the Department of hæmatology, Kings College Hospital, for his permission to report the hæmatological data.

REFERENCES

Aldrich, R. A. Hawkinson, V., Grinstein, M., Watson, C. J. (1951) *Blood*, 6, 685.

Borst, M., Königsdorffer, H. jun. (1929) Untersuchungen uber Porphyrine. Leipzig.

de Marval, L., Pons, R. (1934) *Arch. argent. Pediat.* 5, 220.

Fischer, H. (1915a) *Hoppe-Seyl. Z.* 96, 31.

— (1915b) *Ibid*, p. 148.

— (1916) *Ibid.* 97, 109.

Garrod, A. E. (1923) Inborn Errors of Metabolism. 2nd ed., London.

Gray, C. H., Muir, I. M. H., Neuberger, A. (1950) *Biochem. J.* 47, 542.

— Neuberger, A. (1950) *Ibid*, p. 81.

— — Sneath, P. H. A. (1950) *Ibid*, p. 87.

Grinstein, M., Aldrich, R. A., Hawkinson, V., Watson, C. J. (1949) *J. biol. Chem.* 179, 983.

— — — Lowry, P., Watson, C. J. (1951) *Blood*, 6, 699.

Guenther, H. (1925) Handbuch der Krankenheiten des Blutes und der Blutbildenden Organe. Berlin; vol. II

Lemberg, R., Legge, J. W. (1949) Hematin Compounds and Bile Pigments. New York; p. 510.

London, I. M. (1950) *J. biol. Chem.* 184, 373.

— West, R., Shemin, D., Rittenberg, D. (1950a) *Ibid*, p. 365.

— — — — (1950b) *Ibid*, p. 351.

Mackey, L., Garrod, A. E. (1926) *Quart. J. Med.* 19, 357.

Schwartz, S., Sborov, V., Watson, C. J. (1944) *Amer. J. clin. Path.* 14, 598.

Shemin, D., Rittenberg, D. (1946) *J. biol. Chem.* 166, 621.

Singer, K. (1945) *J. Lab. clin. Med.* 30, 784.

Stich, W. (1950) *Dtsch. med. Wschr.* 75, 1217.

Sveinsson, S. L., Rimington, C., Barnes, H. D. (1949) *Scand. J. clin. Lab. Invest.* 1, 2.

Watson, C. J. (1937) *Arch. intern. Med.* 59, 196.

— (1950) Personal communication.

Weiss, H. (1925) *Dtsch. Arch. klin. Med.* 149, 252.

Medical Societies

MANCHESTER MEDICAL SOCIETY

Control of Bleeding during Surgical Operations

THE section of anæsthetics of the Manchester Medical Society met on March 13 to discuss the control of bleeding during surgical operations.

Dr. C. E. SYKES, opening the discussion, said that the interest of anæsthetists in the methonium compounds was first aroused in 1948 by the experimental work of Paton, Zaimis, and Organe, who found that pentamethonium iodide (c5) intravenously had little effect on a patient who was lying down, but caused a fall in blood-pressure when he stood up. Other workers observed dilatation of the pupil, often persisting for twenty-four hours. The fall in blood-pressure was greater in the hypertensive patient, and vasodilatation was greater in the legs than in the arms. Hexamethonium iodide (c6) seemed more reliable than pentamethonium iodide.

There is no hard and fast rule for dosage, but the systolic blood-pressure should fall to 70 mm. Hg. To achieve this in a healthy adult, 30 mg. may be required, followed when necessary by doses of 20 mg. For old or hypertensive patients 10–20 mg. is usually sufficient.

Posture on the operating-table is important; the site of operation should be the highest part of the body. On return to bed the blood-pressure should be allowed to rise slowly to avoid reactionary hæmorrhage.

Electrocardiographic records have shown no ill effects, but cases with coronary-artery disease should not receive these drugs.

The methonium compounds are normally excreted by the kidney, and consequently they should not be given when renal function is poor. Their use should still be regarded as purely experimental.

Dr. W. B. BACON said that bleeding under anæsthesia could be reduced by controlled hypotension following the use of methonium compounds. These drugs paralyse the autonomic ganglia, and the consequent dilatation of the vascular system has the immediate effect of decreasing peripheral resistance and reducing blood-pressure. Posture is of paramount importance in ensuring a dry surgical field; the site for surgery must be placed at the highest possible level, and sufficient time must be allowed for gravity to drain the blood from this area.

Operations on the head, neck, and thorax are performed with a 20°–30° feet-down tilt. The lateral jack-knife position is used for operations in the region of the hip, and the prone jack-knife for surgery of the spine. For pelvic surgery, after a preliminary "reverse Trendelenburg tilt" to drain blood into the legs, the legs are flexed and the full Trendelenburg position used to drain blood out of the pelvis. Operations in the lithotomy position—e.g., [illegible] difficult, because it is obviously [illegible] the site of surgery at the highest point. Fair results are obtained by using a full Trendelenburg position for some minutes, and by elevating the legs in the stirrups *before* levelling the patient.

During a general anæsthesia combined with hexamethonium the blood-pressure falls first after premedication, then after thiopentone, and finally to 60–70 mm. Hg after hexamethonium. There is no appreciable rise in pressure until four or five hours after administration. Falls in blood-pressure are greatest (and often alarming) in the aged and the hypertensive; the young, nervous, and hypotensive type, on the other hand, is difficult to control. The dose of hexamethonium can be judged only by experience; 0·5 mg. per kg. may be sufficient for the hypertensive, but may have to be increased threefold for the young or nervous patient. A half-dilated pupil may be taken as a sign of adequate dose. The fall of pressure under premedication and thiopentone will give a good indication of the dose required; the larger the fall, the smaller the dose of hexamethonium. Once the ganglia are paralysed, more hexamethonium has no effect.

It is difficult to control blood-pressure by methonium; this is done either by changing the position of the patient—e.g., lowering the head—or by giving pressor drugs—e.g., 'Methedrine.' Methedrine must be given in doses not exceeding 5 mg., well diluted and very slowly, otherwise it may cause a very rapid rise in blood-pressure. The patient must have plenty of oxygen throughout anæsthesia.

Many everyday faults may contribute to the cause of bleeding—for example: hurried induction, or gagging after the short-acting relaxants; a partially blocked expiratory valve; failure to restore full tidal volume when respiration has been depressed by relaxants, or by lithotomy or deep Trendelenburg positions; failure to blunt sensory stimuli from the operation which release adrenaline, so raising the blood-pressure and causing bleeding.

Under hexamethonium the patient is completely devoid of vasomotor control: all movements must be carefully supervised, particularly between the operating-table and the ward. The anæsthetist must see the patient back to bed, and be satisfied with his condition; oxygen must be at hand and the blood-pressure must be carefully watched. A reactionary hæmorrhage might be obscured by the effect of the ganglion block on the pulse-rate, but it would be detected by a fall in blood-pressure.

Dr. M. SWERDLOW wondered whether the production of a bloodless field by means of methonium compounds was just a "clever trick," or did it offer advantages over existing methods of anæsthesia, outweighing any added dangers? He advised caution in the selection of cases, care in the application of the technique, and close supervision of the patient in the immediate postoperative period. The hæmoglobin should always be measured before operation and any anæmia corrected to ensure maximum possible oxygen carriage during the period of hypotension.

He thought that in ear, nose, and throat surgery controlled hypotension was more justifiable; patients are mostly in the younger age-groups, and the site of operation allows a satisfactory anti-Trendelenburg tilt and a high degree of ischæmia.

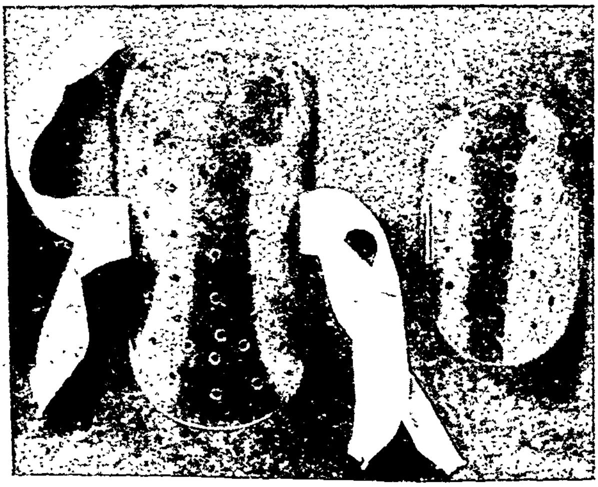
In a general discussion, fears were expressed about the risk of reactionary hæmorrhage, especially when induced hypotension was used in thyroidectomy. Kidney damage may follow prolonged hypotension, and anuria had occurred in some patients. On the other hand, evidence was given to suggest that venous pressure was little affected by the ganglion-blocking drugs, though it fell sharply after loss of blood.

New Inventions

PROTECTIVE SHIELDS FOR ULCER SCARS

THE scar where a so-called "varicose ulcer" has been present often appears to break down if the area is chafed or knocked, and for some time I have been searching for a suitable shield which the patient may wear to protect the vulnerable area.

Such a shield has recently been made for me and is depicted here. Made of 'Perspex,' it may be kept in place with a light garter, or with tapes (see figure). The shield is light, its edges are specially moulded, and the holes with which it is perforated allow of some ventilation. If necessary an elastic stocking can be worn over the shield.



It is not suitable for all persons, but is very useful for selected cases; obviously care must be taken to see that the garter or tapes are not too tight.

The shields have been made by Messrs. J. Drew, 55, Dorset Street, London, W.1.

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Reviews of Books

New Worlds and Old

CHARLES SINGER. London: Heinemann Medical Books. 1951. Pp. 178. 15s.

IN this volume of thirteen essays the doyen of medical historians has put together some thoughts on the frontiers between science on the one hand and philosophy, religion, tradition, and history on the other. Medical readers will be particularly interested in the account of Francis Adams, a Scottish country doctor who was a self-taught classical scholar.

While in practice at Banchory in the wilds of Deeside, Adams produced famous translations of the works of Hippocrates, Paulus Aeginata, and Aretæus the Cappadocian. "His masterpiece *The Seven Books of Paulus Aeginata by Francis Adams* retains to this day its position as far and away the finest venture in pure historical medical research in the English language. It is more than a translation, more than a commentary. The extensive and accurate notes that accompany it trace the practice of Paul backward into remoter antiquity and forward into medieval times. They make it in fact a reference book to the whole history both of Greek and Arabian medicine."

Adams had a peculiar mode of working. When he returned home from his rounds in the late afternoon he would have his supper, collect such books as were specially interesting him, and retire with them at once to bed. He fell asleep immediately and slept for about two hours. He would then awake and work through the night, falling asleep for three or four hours before rising in the morning. He did not begin to see his patients till about ten.

Other readers may prefer the essays on Copernicus, Vesalius, Robert Hooke, Aristotle as a naturalist, or the botany of Theophrastus. They form a stimulating, profound, and readable collection that will add fresh lustre to their author's name.

Ear, Nose, and Throat Diseases for the General Practitioner

WILLIAM MCKENZIE, M.B., F.R.C.S., surgeon, Royal National Throat, Nose and Ear Hospital. Edinburgh: E. & S. Livingstone. 1952. Pp. 133. 9s.

Mr. McKenzie, with past experience of general practice, sets out to put into a small volume such facts as a general practitioner most needs to know about ear, nose, and throat diseases, and to help him give or procure appropriate treatment for patients with these complaints. The book is simply and pleasantly written and the points made are emphasised by case-notes. The general plan is good: common disorders are given suitable priority, and history and symptoms are emphasised rather than signs. These last, indeed, are sometimes neglected: for example, little is said about the appearance of the drums in acute otitis, and nothing at all about that of the throat in carcinoma of the pyriform fossa or the tonsil. Much of the advice (e.g., on the indications for tonsillectomy) is helpful, and there is a justified plea for information in doctors' letters; but some details seem questionable.

"A quinsy," for the author, "is a peritonsillar abscess which has burst or been incised"; and "the expression mastoiditis is limited by otologists to those cases which need operation." Surely a peritonsillar abscess is a quinsy, and inflammation of the mastoid cells is mastoiditis, regardless of course or treatment. Like some other otologists Mr. McKenzie seems scarcely to recognise the very common early acute otitis media of childhood, with pain and fever an hour or so old and a red upper half of the drum. Before chemotherapy many such ears went on to discharge or needed myringotomy, while some progressed to mastoiditis; now almost all subside quickly and lastingly with sulphonamides; (penicillin, with its needle pricks, is rarely required). The subacute catarrhal otitis of childhood with recurrent slight earache and deafness is mentioned only as a symptom of adenoid infection. Epistaxis and its treatment are described without regard to the patient's age: "If the bleeding has not stopped the patient should be sent to bed and given morphia gr. $^{1}/_{4}$ at once." Perhaps no general practitioner would apply this advice to a child, but even for an adult compression of the nostrils while sitting up might be worth trying. It is hard to believe that "Eustachian catheterisation is successful only in a few cases of middle ear deafness caused by infection."

With revision this book, at present unequal, might become a very good one.

A Dictionary of Antibiosis

Leonard Karel and Elizabeth Spencer Roach. New York: Columbia University Press. London: Oxford University Press. 1951. Pp. 373. $8.50. *55s.*

The authors of this useful work are members of the staff of the Division of Research Grants, in the National Institutes of Health of the United States Public Health Service. They have winnowed the scientific publications of the world for information about the search for antibiotics. The result is a list of the several thousand plants from which antibiotics have already been sought, the microscopic test organisms used, the methods of extraction, the substances extracted, and the chemical and physical properties, and the ranges of organisms against which they are effective or ineffective, either in vivo or in vitro. The references are given in a bibliography, and the volume should be very valuable in preventing waste of time and effort of investigators in this field.

Die Innersekretorischen Krankheiten des Kindes und ihre Behandlung

Professor Dr. Erwin Thomas, late medical director of the City Hospital for Women and Children (Keetmans foundation) Duisburg. Stuttgart: Ferdinand Enke. 1951. Pp. 136. D.M. 12.40.

Professor Thomas has long been well known for his contributions to German textbooks and other publications. In this little book he attempts to review, for the pædiatrician, the progress of endocrinology over the last ten years. He describes the functions and diseases of the sex glands, pancreas, suprarenals, thyroid, parathyroids, thymus, pituitary, and pineal gland and mentions many other conditions of more uncertain origin. A great many facts are given in a small space, but the resultant telegraphic style does not make for easy reading. The exhaustive reference list and the frequent quotation of opposing views indicate how often many current assumptions are questionable. The discussion of diseases not obviously endocrine in origin, such as resistant or renal rickets, Fanconi syndrome, and cystinosis, illustrates the tendency to attempt too much. On the other hand, the amount of necessarily incomplete information is in itself a spur to further study.

Portrait of a Surgeon

Ernest A. Gray, senior bacteriologist in the National Agricultural Advisory Service. London: Robert Hale. 1952. Pp. 219. *16s.*

This biography of John Hunter seems to be a mixture of fact and fiction; nor is it easy to distinguish them, for the facts are by no means all correct. William Cheselden is referred to throughout as Richard. Matthew Baillie and Sir Richard Croft are stated to have married the daughters of John Knyveton, whereas really they married the daughters of Thomas Denman. The real surprise of the book is the introduction, as a "lifelong friend" of John Hunter, of this John Knyveton, with extracts from an alleged diary which we strongly suspect is wholly or mainly fictitious, and centred in the life of Denman (as seems to be borne out by the reference in the index to "Denman vide John Knyveton.") The author has elsewhere admitted that Knyveton is an imaginary name, and has described the "diary" as "an expansion of an original document that is not of great length" and as "an expansion of the preface of a famous 18th century work." He has never to the best of our knowledge published the bare original text (though he has now expanded it to three full-length books). It is quite unjustifiable to incorporate material of this kind in what pretends to be an authentic biography; but if the book is not regarded as a serious biographical work, and its oddities are overlooked, it is interesting and readable.

The Physician: *As man of letters, science and actio* (2nd ed. Edinburgh: E. & S. Livingstone. 1951. Pp. 25 *21s.*).—This short book by Prof. T. K. Monro will be usefu to the student of the history of medicine. It brims over wit facts about doctors of all periods and races, presenting, i scholarly and pithy English, an epitome of internation medical biography.

The Merck Index of Chemicals and Drugs (6th ed Rahway, N.J.: Merck & Co. Inc. 1952. Pp. 1167. $7.50).— This elegant edition of a reference book which first appeare in 1889 has been revised to include the advances of the past 1 years. Sections on the properties and uses of radioactiv isotopes are among the new features which will commend i to those who seek concise and up-to-date information on th chemistry of drugs. The binding, we are told, is resistant t mildew: but the other qualities of the book make it unlikel that it will be neglected long enough to put this particular on to the proof.

Tuberculosis Among Children and Adults (3rd ed Oxford: Blackwell Scientific Publications. 1951. Pp. 89 £4 *15s.*).—Those who favour the use of B.C.G. for protecti inoculation against tuberculosis will find in this volume clear statement of the "other side of the question," fo Prof. J. Arthur Myers places great reliance on the value of naturally occurring Mantoux-positive reaction in tuberculosi control and prevention. B.C.G., in his opinion, not only ha intrinsic limitations, but by inducing a positive tuberculi test makes it impossible to distinguish the infected from th uninfected. The third edition of his book has not so muc been revised as extended; all the modern work since 193 is collected in part IV, new to the book, and occupying abou half of it. Collaborators have added chapters on treatment b artificial pneumothorax, thoracoplasty, and lung resection It is, however, in the sphere of epidemiology that the interes of this book lies, and the reader will learn much from it abou one section of American opinion.

A Doctor's London (London: Allan Wingate. 1952. Pp. 112. *13s. 6d.*).—This interesting and entertaining book has been written with relish by a well-known doctor who is also a scholar and a journalist, and who uses the pseudonym of Harvey Graham. He gives a lively account of many features of London medical life, including Harley Street, the Hunterian Society, the Royal College of Surgeons, the National Institute of Medical Research at Mill Hill, and the Royal Hospitals, interspersed with historical details, engaging stories, and a remarkable series of illustrations. Not the least interesting sections deal with lesser-known places such as the licensed houses "The Rose of Normandy," and "The Book," whose proprietor was responsible for the advertisement "If anyone asks you where the British Museum is, it's opposite 'The Book.'" The personalities are as varied. William Hunter working in his school of anatomy, now the stage of the Lyric Theatre; Rahere; John of Mirfield; Dr. Graham, the most famous of all charlatans; Mary Toft, the rabbit-breeder; Daniel Lambert, who weighed 52 st.; giants, dwarfs, centenarians, and hypnotists. The omission of any real account of the Royal College of Physicians seems remarkable and the author has some tendency to use slang words unnecessarily and to wander far away from London. But anything can be forgiven to a teller of good stories.

Textbook of Pharmacognosy (2nd ed. London: J. & A. Churchill. 1951. Pp. 556. *35s.*).—The scope of pharmacognosy (literally the knowledge of drugs) is wide and difficult to define. At first sight it looks like a synonym for materia medica; and Hale-White, in his classical work on that subject, described it as "*materia medica proper . . .* the knowledge of the natural history, physical characters, and chemical, properties of drugs." Mr. T. E. Wallis, on the other hand, distinguishes four departments of the study of drugs—pharmaceutical chemistry; pharmacy or pharmaceutics; pharmacology or pharmacodynamics; and pharmacognosy, which he defines as "the scientific study of the structural, physical, chemical, and sensory characters of crude drugs of animal and vegetable origin, including their history, cultivation, and collection and . . . *other treatment they receive* . . . from the producer to the distributor or pharmacist." His book contains careful and detailed descriptions, macroscopical and microscopical, of the traditional drugs in their crude (i.e., natural) state, generously illustrated with admirable line drawings. The final sections, on the commercial aspects, including cultivation, insect pests, adulteration, and standardisation, are brief but succinct.

THE LANCET

LONDON: SATURDAY, APRIL 26, 1952

Cœliac Disease and Wheat

For many years it has been customary to treat cases of the cœliac syndrome with diets devoid of complex carbohydrates such as starch. This dietetic therapy was based on clinical observation rather than on metabolic studies. Wilfrid Sheldon,[1] in twelve-day fat-balances on 15 patients, found that removal of starch from the diet was associated with a significant rise in fat absorption; and dextrin behaved like starch.[2] This work was confirmed and extended by May,[3] who before the war had shown that rich sources of vitamins of the B complex, such as yeast, improved the absorption of vitamin A in cœliac disease. He noted that the defect in fat absorption when cereal was given persisted despite the administration of the B complex and was accompanied by retention of sodium and even greater retention of chloride.

Unfortunately in these and other studies the content of complex carbohydrate in the diet was not the only factor that was varied: when starch was eliminated so was wheat gluten. The significance of this has now been made apparent by two very important studies from Holland. Starting with observations in the famine from September, 1944, to May, 1945, when wheat and rice were not to be had in the Western Netherlands, Dicke[4] noted that patients with cœliac disease improved when wheat and rye flour were excluded from their diet but could nevertheless tolerate large quantities of wheat starch, potatoes, or rice-meal. In fact, the intolerance was not to starch but to some other substance present in wheat flour. The work of van de Kamer and his associates in the Central Institute for Food Research in Utrecht has supplemented the findings of Dicke. Thus Weijers and van de Kamer[5] have studied fat absorption in normal and abnormal infants and children with special reference to the cœliac syndrome. Their technique is essentially to determine changes in blood-lipids after an oral test dose of fat—estimating blood-fat, vitamin A, and chylomicrons—and to determine fat in the fæces. By "absorption" is meant the difference between fat ingested and fat excreted: they emphasise that in a normal human being the fæcal fat consists for the greater part of endogenous fat. In the cœliac syndrome butter-fat which is composed mainly of the higher saturated fatty acids, was not well tolerated; for in this condition the saturated fatty acids are badly absorbed, whereas the unsaturated fatty acids are almost completely absorbed. When these patients were given olive oil, which contains only 10% of saturated fatty acids, most of the fat was absorbed and the condition was much improved. Unlike the normal child, therefore, the cœliac patient has a different degree of toleration for fatty acids of different saturation. When they proceeded to follow up Dicke's observation on the injurious effect of wheat flour, the Utrecht workers found that the presence of wheat flour in the diet did not affect the absorption of unsaturated fatty acids but did increase the excretion of saturated fatty acids: indeed, when olive oil and wheat flour were given to patients with cœliac disease much greater quantities of saturated fatty acids were excreted than were ingested. Even on a fat-free diet the patient excreted fat, if his food included wheat flour. In three cases investigated, nicotinamide counterbalanced the injurious effects of wheat flour.

van de Kamer and his associates concluded that a defect in absorption would not explain the facts, and that in cœliac disease there must be some disturbance in the intermediate metabolism of fat—a disturbance particularly affecting saturated fatty acids. But Professor Frazer and his team at Birmingham, whose paper we are happy to publish this week, reach a different conclusion. They fully agree about the great improvement in patients with cœliac disease whose diet is freed from wheat flour; and they have notably extended the observations of Dicke and of Weijers and van de Kamer by showing that it is the gluten of wheat flour that is injurious. (The various clinicians who have obtained benefit by decreasing dietary starch have done so, it appears, because they have unwittingly decreased dietary wheat gluten at the same time.) The difference of opinion concerns not the facts but the explanation of them. Frazer and his colleagues—on the basis of their partition hypothesis that fatty acids of hydrolysed fat are absorbed into portal blood whereas a fine emulsion of unhydrolysed fat passes to the lymphatic system through the lacteals—explain the steatorrhœa of cœliac disease as being caused by decrease dabsorption, possibly through increased formation of mucus. The Utrecht workers, on the other hand, may still be unwilling to accept this; and although they have been careful not to criticise the partition hypothesis as the normal mechanism for absorption of fat, it has come under a certain amount of bombardment elsewhere. Ivy[6] found no indication that, after ingestion, finely emulsified mineral oil appeared in the thoracic-duct lymph of dogs; and studies with C^{14}-labelled fatty acids have not yet confirmed this hypothesis.

Meanwhile, allowing the Utrecht and Birmingham schools, along with others in Madrid and the United States, to debate the mechanism of fat absorption and the metabolism of fatty acids, we can all be thankful for the new knowledge that the child with cœliac disease will show spectacular improvement if wheat or rye flour is removed from the diet. As wheat is the largest dietary source of vitamins of the B complex, and as May showed the value of these to the cœliac child and the Utrecht workers emphasise the importance of nicotinamide, the clinician must ensure the supply of these vitamins from other sources such as dried yeast or liver. But with this proviso, he may hope for good results from this dramatic advance in treatment which we owe to our Dutch colleagues. And the Birmingham investigations encourage the hope of further developments.

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[1] Sheldon, W. P. H. *Arch. Dis. Childh.* 1949, 24, 81.

[2] Sheldon, W. P. H., MacMahon, A. *Ibid*, p. 245.

[3] Lowe, C. U., May, C. D. *Amer. J. Dis. Child.* 1951, 81, 81.

[4] Dicke, W. K. Cœliakie. Utrecht M.D. thesis. 1950.

[5] Weijers, H. A., van de Kamer, J. H. De vetresorptie van gezonde en zieke zuigelingen en kinderen in het bijzonder van cœliakiepatiënten. Centraal Inst. v. voedingsonderzoek. T.N.O. Publication no. 113. Utrecht, 1950.

[6] Berry, I. M., Ivy, A. C. *Amer. J. Physiol.* 1950, 162, 80.

Cancer Surveyed

In 1935 the British Empire Cancer Campaign set up a clinical research committee to collect accurate information about the efficacy of various forms of treatment and the proportion of cases cured by each method alone or combined. By 1938 a scheme for discovering these facts had been devised; and fifty thousand standard case-sheets, for various regions of the body, were distributed to hospitals in the County of London, all of which had agreed to send in a completed form for every case of cancer seen. Each hospital had a cancer registrar; and the Campaign appointed Lieut.-Colonel W. L. HARNETT as full-time medical secretary and registrar, charged with the task of coördinating and interpreting the data. By the end of 1938, 8480 case-sheets has been returned. On the outbreak of war, however, in September, 1939, the hospitals were dispersed out of London, the registrars joined various services, and collection of fresh cases came to an end. It might have been thought inevitable that the whole scheme should be dropped or postponed until more propitious times. But 15,200 cancer cases had by then been registered; so a small emergency committee was formed to meet regularly and to code, tabulate, and follow up these cases as far as war-time conditions allowed. During the next few years the Campaign's annual reports contained preliminary accounts of cancer of the breast and of the cervix and corpus uteri; and since then eight more have appeared. A five-year follow-up period ended in 1944. All but 400 (2·63%) of the 15,200 registered cases have been traced. A most impressive Survey of Cancer in London has now been published.[1]

The survey deals with forty-four separate anatomical sites of cancer. The data concern the number of patients, their age-distribution, hereditary factors where known, occupation, social class, relevant past history, the first symptom, the interval before first consulting a doctor and before the first special examination, the advice and treatment before admission to hospital, and the findings and treatment after admission, together with the five-year survival-rate and pathological findings. Sex-ratios are given, and the ratios of single to married and parous women. To this great wealth of valuable material a novel feature has been added. This is an actuarial estimate of duration of survival for each method of treatment. These estimates are for various reasons only approximate, but it is of great value in making decisions about treatment to be able to assess even roughly what proportion of the natural expectation of life may be hoped for as a result of different methods. The figures indicate that even with glandular and general metastases survival-time is doubled by palliative treatment either by surgery or by radiotherapy. The survey was begun before stilbœstrol came into use in this country; and, as time goes on, it will be useful to base estimates of cure on a survival-rate reckoned longer than five years after the start of treatment. The survey includes survival-times of some untreated cases, which provide a reminder for believers in secret remedies and wonder drugs that the natural progress of cancer is not uniform or necessarily continuous and rapid.

One of the many valuable features of this survey is the comparison throughout with previously collected figures, including those of the Registrar-General. This is especially necessary in comparing incidence in different social classes; a purely hospital population consists, or did in the past, mainly of classes III–V—namely, skilled, intermediate, and unskilled workers. The former occupations of a large group of people labelled retired require in future to be detailed; and a plea might be entered for more exact information about lactation in parous women with breast cancer, to determine whether this function was normal. The Registrar-General's figures have revealed quite an appreciable amount of preventable cancer, and the Campaign's registrars, who actually meet the patients, have the opportunity to disclose even more.

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[1] British Empire Cancer Campaign. A Survey of Cancer in London. 1952. Pp. 834. 45s. Obtainable from the Campaign, 11, Grosvenor Crescent, London, S.W.1.

Restrictions in Heart-disease

"Many physicians appear to be too strict and particular in the rules of diet and regimen, which they deliver as proper to be observed by all who are solicitous either to preserve or recover their health. The too anxious attention to these rules hath often hurt those who are well, and added unnecessarily to the distresses of the sick." These words by HEBERDEN[1] are quoted by Dr. ROBERT LEVY at the start of a paper on Needless Restrictions Imposed on Cardiac Patients.[2]

Dr. LEVY remarks that "any person with a disorder of the heart or circulation, regardless of its cause or the degree of functional impairment, too often is looked upon as an invalid. His condition is a cause for concern. Accordingly, it is common practice to classify him as unfit to pursue his customary way of living and advise that he follow regulations which, in varying degree, restrict his activities and curtail his pleasures." He then proceeds "to consider the basis for some of these restrictions and to inquire into the reasons why physicians are so ready to impose them." Starting with tobacco, he remarks that estimation of cardiac work (with the low-frequency, critically damped ballistocardiograph) shows that tobacco causes little change in the cardiovascular system; and it rarely causes anginal pain, even in those liable to it. Nevertheless in congestive heart-failure, the acute stages of cardiac infarction, and active rheumatic fever it should be forbidden utterly, because the slightest increase in the work of the heart has to be avoided, and in peripheral vascular disease it should also be forbidden because of its constricting action on peripheral vessels.[3] Climbing stairs is another activity traditionally forbidden to patients with heart-disease; but ballistocardiographic studies[4] have shown that this does not greatly increase the work of the heart, and these patients may be allowed to take stairs leisurely, at a pace which they find agreeable; deliberate retardation, like hurry, may augment cardiac work. In the presence of congestive failure, however, or if anginal pain comes on during exertion, stairs should be avoided. As regards air travel, Levy concludes that the vast majority of cardiac patients may undertake this without undue risk. Between 1930 and 1949 91 million passengers flew on United States air routes with only 49 in-flight deaths attributed to heart-disease, although a considerable number of cardiac patients fly from outlying districts or foreign countries to a medical centre for treatment.[5] Levy suggests that this figure is little, if any, greater than might be found in this same group of people on the ground; and except for cases of congestive failure, active carditis, cardiac infarction with onset in the previous three months, or severe angina he does not forbid flying. What hazards there are in air travel are due not so much to the hypoxia of flight as to the excitements, delays, or discomforts incidental to flying.[6]

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[1] Heberden, W. Commentaries on the History and Cure of Diseases. London, 1802.

[2] Levy, R. L. *Circulation*, 1952, 5, 451.

[3] Levy, R. L., Mathers, J. A. L., Mueller, A., Nickerson, J. L. *J. Amer. med. Ass.* 1947, 135, 417. Mathers, J. A. L., Patterson, M. C., Levy, R. L. *Amer. Heart J.* 1949, 37, 612. Levy, R. L. *Med. Clin. N. Amer.* 1950, 34, 697.

[4] Mathers, J. A. L., Griffeath, H. I., Levy, R. L., Nickerson, J. L. *Circulation*, 1951, 3, 224.

Of all restrictions imposed on heart patients, curtailment of normal employment or recreation is the most usual and the most disheartening. Most cardiac patients can work and in fact do so[7]; and when selectively placed in industry their attendance records have been as good as the U.S. national average for all industrial workers.[8] With the obvious exceptions (active rheumatic carditis, chronic congestive heart-failure, or intractable angina) cardiac patients are better off in health, wealth, and happiness if they are allowed to work. The same applies to exercise; and the patient himself is the best judge of what unduly strains his circulation. Those who are accustomed to exercise need not sacrifice their golf, fishing, riding, or swimming, though squash, for the majority, is too strenuous. Sir John Parkinson[9] has remarked: "Modern medical opinion allows children with congenital malformations of the heart to participate in any and every form of activity which they can undertake without distress. It does them good, not harm, and these children will not hurt themselves. Many adults might with advantage follow the same rule in regard to their handicap." Williamson[10] even suggests that in the child convalescent from rheumatic fever exercise prevents mitral stenosis.

An irksome restriction for many cardiac patients confined to bed is the use of the bedpan; and Levy concludes that for "comfort, degree of effort and esthetic satisfaction, the commode is to be preferred." This is supported by evidence[11] that significantly more energy is expended on the bedpan than on the commode.

In recent years dietary restrictions have been increasingly in vogue for cardiovascular patients, particularly those with atherosclerosis, congestive heart-failure, and hypertensive heart-disease. The low-fat low-cholesterol diet has been recommended as a means of arresting atheromatous vascular disease, because cholesterol is found in atheromatous lesions and raised cholesterol values may be present in the serum of patients with coronary heart-disease. Levy insists that there is no justification for enforcing this tedious diet on such flimsy evidence. Cholesterol can be synthesised from the acetate precursor in protein and carbohydrate, and moreover in many cases of atheroma the cholesterol and lipids in the serum are not raised. Low-salt diets are of proved value in congestive heart-failure, although if mercurial diuretics are also given there is some danger of hypochloræmic alkalosis or of sodium depletion. Levy suggests that in milder cases of congestive heart-failure food may be normally seasoned in the kitchen; all that is necessary is to eschew the salt-cellar at table and to avoid bacon, haddock, and other very salty items. The use of a rigidly salt-free diet for hypertension is hardly justifiable, since the evidence for its value is unsatisfactory. Turning from treatment to diagnosis, Levy emphasises that the electrocardiograph does not measure the capacity of the heart for work, and that if it deviates somewhat from the normal there is no need to order a programme of restricted activity and so create a cardiac invalid. He cites the case of a man who since a coronary thrombosis in 1946 has had complete auriculoventricular block, right bundle-branch block, and auricular fibrillation, and who yet has pursued an active and satisfying life as a business executive.

Why do doctors restrict patients when neither clinical nor laboratory evidence supports them? Levy suggests four reasons. Firstly, doctors seize eagerly on any measure which sounds promising, because they are often uncritical of, or unfamiliar with, the reasons which led to its proposal. Secondly, the patient expects his régime to be modified and is disappointed if he is told to carry on exactly as before. Thirdly, the doctor "aims to protect himself from criticism. If restrictions are imposed on the patient and these are not heeded, no blame can be placed on the doctor should the course be unfavourable or should the patient die. Conversely, if improvement occurs, this is ascribed to having followed the advice given." Fourthly, a great deal of pressure is exerted by the laity, who get their ideas from daily papers and popular magazines which retail unproved theories or unreliable observations as established facts. The patient expects the doctor to subscribe to what he himself considers the latest observations. Levy quotes Bernard Shaw, who wrote in his preface to *The Doctor's Dilemma*: "The doctor may lay down the law despotically enough to the patient at points where the patient's mind is simply blank; but when the patient has a prejudice the doctor must either keep it in countenance or lose his patient." Under such circumstances, at the expense of additional time and effort, the physician should assume the rôle of educator.

Our function as physicians is to promote the health of those who come to us for help; in our zeal to prolong life let us not, without good cause, lessen their joy in living. Dr. Levy's plea for more enlightened treatment of cardiac patients should remind us not only that "a little of what you fancy does you good" but that a lot of what you do not fancy does you harm.

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[5] Tillisch, J. H., Stotler, J. F., Lovelace, W. R. *J. Aviation Med.* 1943, 14, 162.

[6] McFarland, R. A. Human Factors in Air Transport Operations. New York (in the press).

[7] Kresky, B., Goldwater, L. J. *Amer. Heart J.* 1914, 27, 623. Goldwater, L. J. *Rhode Island med. J.* 1947, 30, 179.

[8] *Circulation*, 1951, 3, 289.

[9] Parkinson, J. *Lancet*, 1951, ii, 457.

[10] Williamson, B. *Brit. med. J.* 1948, i, 26.

[11] Benton, J. G., Brown, H., Rusk, H. A. *J. Amer. med. Ass.* 1950, 144, 1443. Annotation, *Lancet*, 1950, i, 551.

Annotations

THE SEARCH FOR VIRICIDES

SOME of the larger viruses, such as the psittacosis-lymphogranuloma group, are susceptible to chloramphenicol and other antibiotics, but there is no solid evidence that any drug is effective against the smaller viruses which attack man. Many compounds have been tested on experimental virus infections in the chick embryo, but the results do not always tell us how they will act in patients. Eaton and his colleagues[1] at Harvard have demonstrated that the aromatic diamidines will inhibit virus growth in the chick embryo. Pentamidine had some in-vitro viricidal effect on feline pneumonitis and meningopneumonitis but no action on influenza and mumps viruses. Stilbamidine had a selective effect on mumps virus in the allantoic sac, which suggests that the drug does not act simply in virtue of its toxicity to tissues in general. Tissue-culture experiments with mumps and influenza viruses have led the Harvard workers[2] to believe that the diamidines act directly on intracellular virus or set up a chemical blockade which affects a tissue component essential for virus synthesis.

In Sweden, Fischer[3] has been investigating the antiviral activity of extracts of various fruits and vegetables, including bilberry, red and black currant, horse-chestnut, spinach, onion, carrot, and potato, against one of the *Bact. coli* bacteriophages. The most potent of the extracts tested was one derived from maple fruit. This completely and rapidly destroyed the bacteriophage and, in certain dilutions, selectively destroyed the phage leaving the bacterium apparently undamaged. The active substance is insoluble in alcohol, ether, or acetone but soluble in water; it can be filtered and heated to 120°C for 10 minutes without loss of potency. Fischer is already testing it against the Lansing strain of poliomyelitis virus, and we clearly need more information about its effect on bacteriophage.

Some of the structural analogues of the purine and pyrimidine constituents of nucleic acid inhibit the multiplication of vaccinia virus in chick-embryo tissue. In the U.S.A., Thompson and colleagues[4] have investigated a series of 5-phenoxythiouracils and related compounds and find that they have little in-vitro activity but can be shown to have a definite protective effect in vivo if treatment is begun soon after infection. The treated animals have a lower titre of virus in their tissues than the controls, suggesting that these substances directly or indirectly retard virus multiplication but are not true viricides. The most effective of the 5-phenoxythiouracils has no antithyroid or antibacterial action at concentrations which inhibit the growth of vaccinia virus, nor does it affect other viruses. Groupé and colleagues[5] are searching for antiviral substances among the products of the actinomycetes, already a prolific source of antibiotics against bacteria. Of 113 culture filtrates tested against the viruses of Newcastle disease and influenza, 8 prolonged the life of infected embryos by 24 hours or more, and 3 prevented the death of more than half of the inoculated eggs. A strain of *Streptomyces lavendulæ* not producing streptothricin has yielded a substance named 'Ehrlichin,' which inhibits influenza viruses A and B and the Newcastle disease virus if it is allowed to act for 2–3 hours before the eggs are inoculated. Ehrlichin had a definite inhibitory effect in vivo only on influenza-B infections, and its suppressive effect on the formation of viral hæmagglutinin was reduced when it was injected before, instead of after, infection of the eggs. Ehrlichin is a crude substance, and the solutions used may contain more than one antiviral agent; but there is no doubt about its activity against some viruses. In-vitro serum destroys its activity, but nevertheless it slightly reduces the pulmonary consolidation produced by virus infections in mice. Against representative species of bacteria, fungi, the pox group of viruses, and bacteriophage ehrlichin is completely inactive.

These diverse studies are not of much immediate practical importance, but they show that the viruses have chinks in their armour and each chink is being energetically explored.

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[1] Eaton, M. D., Levenson, C. G., Perry, M. *J. Immunol.* 1952, 68, 1.

[2] Eaton, M. D., Perry, M. E., Levinson, C. G., Gocke, I. M. *Ibid*, p. 321.

[3] Fischer, G. *Ann. Inst. Pasteur*, 1952, 82, 119.

[4] Thompson, R. L., Price, M., Minton, S. A., Falco, E. A., Hitchings, G. H. *J. Immunol.* 1951, 67, 483.

[5] Groupé, V., Frankel, J. W., Lechavalier, M., Waksman, S. A. *Ibid*, p. 471.

COÖRDINATION OF THE HEALTH SERVICE

IMPRESSED by the need for closer integration in the National Health Service, the Central Health Services Council set up a committee, under the chairmanship of Mr. F. Messer, M.P., to study how this might be achieved; and the committee has now reported.[1]

The report remarks that the problem is especially difficult for three reasons. In the first place, two of the three main branches of the service—namely, the hospital and general-practitioner services—have not in themselves a unitary structure. Secondly, two of the branches are associated with authorities which are not created by the Act but which are closely concerned with its operation: in the hospital service both boards of governors and regional boards have a special relation to the universities, while the local health authority services are closely related to county and county-borough councils. Thirdly, there is the difficulty of numbers and geography; the geographical pattern is so complex that one authority must find it hard to be conscious of its "opposite number." Yet it would be wrong to conclude that the structure of the service is wholly to blame for the failure of the various authorities to coöperate more effectively; the need for coördination has been emphasised but not created by the National Health Service; and it is unreasonable to expect perfect coördination in so vast a concern.

> "Over half a million people are engaged in the Service. It is the third largest concern in the country. Many organisations which have a much more unitary structure and a more strictly utilitarian purpose have suffered from their own severe problems of internal organisation and have had to examine in the same way the relative advantages of geographical and departmental devolution. All concerns which surpass the grasp of one individual reveal difficulties of internal coördination and integration. The central planning staff can do a certain amount but the greater the delegation to the periphery, the greater the problem of maintaining internal cohesion."

With this reservation the committee states flatly that it is dissatisfied with present arrangements for coöperation; and it describes in detail the various ways in which the need is not being met. Turning to remedies, the report finds no hope of substantial improvement from extension of "interlocking" membership, exchange of papers, ad-hoc Ministry circulars on particular problems, ad-hoc coöperation between officers, ad-hoc meetings, or standing joint committees on special subjects. With each of these rejected in turn, the committee came, by elimination, to the solution of standing joint consultative committees; and it has given thought to the constitution of such bodies. Logic, it declares, would demand the creation of a regional committee midway between the national advisory machinery and committees at local level. Yet only the hospital service has any regional authority; and a regional committee, if it were to be fully representative, would be unwieldy, while if its size were kept within reasonable bounds direct representation would be denied to some authorities. The committee therefore concentrated its attention on coördination at the level of the local health authority, executive council, or hospital management committee. Here again it found itself in difficulties over the definition of areas; for the catchment areas of hospital management committees are seldom coterminous with the area of the local health authority and executive council. In the end the committee concluded that:

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[1] Central Health Services Council: Report on Coöperation between Hospital, Local Authority, and General Practitioner Services. H.M. Stationery Office. Pp. 34. 1s. 6d.

(a) The county borough or other large town should usually be the centre on which a committee is based.

(b) Since the county population almost always makes extensive use of hospital services within the county borough, both the county and the county borough and the two executive councils should be represented on the one committee.

(c) A combination of hospital management committee catchment areas or of areas of county-council divisional health areas with the county boroughs they adjoin will usually prove the most satisfactory arrangement, but wherever possible a local health authority boundary should be used (this will only be a county-borough boundary in the larger cities).

In these "local health service areas" membership of the "joint health consultative committees" might be drawn one-third from the hospital management committee(s) providing general hospital services, one-third from the executive council(s) and the local medical committee, and one-third from the county and/or county borough concerned. The functions of these committees would be: (1) to discuss local arrangements of mutual concern; and (2) to receive early information of major developments and to suggest modifications thought desirable. The local health service areas might be decided by regional conferences, to be convened by regional hospital boards; and "some of us consider that the regional conference, having once met, may prove too useful to be allowed to disappear altogether."

The committee frankly owns that "we are well aware of the danger . . . of creating another series of committees in a Service in which no one wants more of them"; but it rightly goes on to say that the problem of coördination can no longer be allowed to drift, "only to be tackled in places and at times where personalities permit and where pressing questions demand." It foresees that the proposed new committees can be fashioned after no single pattern; and the task of the regional conferences is likely to be far from easy.

SKIN REACTIONS TO ADHESIVE DRESSINGS

THE ever-increasing diversity of adhesive bandages, plasters, and dressings provides a range which, from cosmetic and æsthetic aspects, should satisfy all tastes. Nowadays dressings, in workaday buff or white or flesh tints, are second only to cosmetics in their spectral range. They are made rigid or elastic with one-way or two-way stretch, ensuring adherence and conformity to all but the most awkward of anatomical contours. The exposed surface may, like a photographic print, be matt or glossy, and the corners may be as rectangular as a football field or as delicately curved as a race-track.

Less attention seems to have been paid to making sure that these devices shall not upset the skin. Skin reactions are not only a nuisance but may cause considerable suffering and invalidity from spreading sensitisation. There is still no satisfactory answer to the question: What is the best kind of adhesive to apply to sensitive skin? When the application of an adhesive dressing has to be continued for a long time, as with extension plasters, or indefinitely, as in treating hypostatic ulcers or affixing a Koenig-Rutzen or "disposable plastic" ileocolostomy bag, the onset of soreness is generally taken as an indication for discontinuing adhesive bandages or dressings, at least for a time. In such cases, some irritating or sensitising property of the adhesive is usually blamed; but common causes of trouble are interference with sweat evaporation by impermeable adhesive materials, and sweat retention within the epidermis owing to the blockage of sweat-duct ostia by keratotic material produced by the stimulating effect of the adhesive material on the epidermis. Interference with evaporation of sweat causes the skin to become white and sodden; and wounds under such dressings become moist, lose their sealing scab, gape, and heal slowly. Keratotic plugging of the ostia leads to the escape of sweat under pressure from the sweat-ducts into the epidermis. This causes disruption of the epidermal cells, an inflammatory reaction, and itchy red papulation similar to miliaria rubra (prickly heat).

Peck et al.[1] conclude that three types of reaction may follow application of adhesive tape: a fleeting reaction from the trauma of removal, a reaction of irritation, or a reaction of eczematous sensitisation. The relatively unimportant reaction of traumatic removal occurs particularly when the adhesive is tacky, and it can be minimised by careful removal and by the use of solvents. The reaction of irritation, which is the commonest type, occurs only after five days or longer; and the histological changes are very similar to those of miliaria rubra—namely, plugging of the sweat-duct orifices with keratin and some generalised hyperkeratosis, affecting even the sebaceous follicles. O'Brien[2] thinks that closure of the sweat-pores in prickly heat is due to several factors, including staphylococcal infection, the use of fat solvents, sebaceous deficiency, and possibly œdema of the stratum corneum. Shelley et al.[3] believe that minor epidermal injury from chemical or physical causes contributes to the production of miliaria rubra. Thus adhesive tape or even the maceration from sweat itself may produce hyperkeratosis and plugging. It takes three days for the keratin plugs to form within the sweat-duct orifices. This seems consistent with Peck's observation that the reaction of irritation takes five days or more to develop; but Peck et al. believe that keratin stimulation with a miliaria-like effect cannot alone account for the reaction of irritation. They think that other factors are bacterial multiplication under the plaster in conditions of maceration and alteration of pH towards alkalinity. The third type of reaction—sensitisation to the adhesive—is rare. The histological changes are identical with those of allergic contact dermatitis. Peck et al. obtained from three manufacturers of adhesive dressings data on no less than 28 ingredients of adhesive plasters; and they found negative patch tests to each single ingredient in people who had previously proved hypersensitive to the adhesive plaster. They suggest that this seeming anomaly was due either to batch variations or to the presence in the completed plaster of chemical compounds differing in their sensitising potentialities from those of the several ingredients.

Schilling et al.[4] have carried out controlled clinical trials with micro-porous 'Nylon' film dressings in the treatment of minor wounds. Such dressings provide an effective barrier against micro-organisms but are sufficiently permeable to water vapour to prevent the skin from becoming sodden. They found that the average healing-time for 19 clean wounds treated with nylon dressings was 6·26 days, and for 18 clean wounds dressed with the usual waterproof dressings 9·06 days. In oil-contaminated wounds the times were 5·87 days in 31 cases treated with nylon dressings, and 8·07 days in 30 cases treated with waterproof dressings. The seal was maintained in 78% of 121 nylon dressings, but in only 40% of 92 waterproof dressings because of the tendency to replace this type periodically in an attempt to minimise maceration.

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[1] Peck, S. M., Michelfelder, T. J., Palitz, L. L. *Arch. Derm. Syph., Chicago*, 1951, 63, 289.

[2] O'Brien, J. P. *Brit. J. Derm.* 1947, 59, 125; *J. invest. Derm.* 1950, 15, 95.

[3] Shelley, W. B., Widman, F. D., Pillsbury, D. M. *J. invest. Derm.* 1948, 11, 275. Shelley, W. B., Horvath, P. N. *Ibid*, 1950, 14, 9, 193. Shelley, W. B. *Ibid*, 1951, 16, 53.

[4] Schilling, R. S. F., Roberts, M. Goodman, N. *Lancet*. 1950, i, 293.

The aim of manufacturers, then, must be to provide adhesive dressings which permit sweat evaporation yet prevent contamination by bacteria, which cause little epidermal keratinisation, and which have a low potential of eczematous sensitisation. It is gratifying to know that leading firms are working on these lines with perforated elastic materials, porous spreading of adhesives, and micro-porous coverings. It has been suggested that an antiseptic should be incorporated in the adhesive for sweat-retaining dressings, as a means of inhibiting bacterial flora. In practice, however, this might lead to an increased incidence of eczematous sensitisation. The problem is by no means easy. It may be that an adhesive, because of its sticky properties, must inevitably have some keratin-stimulating effect.

ACETYLCHOLINE IN ANXIETY STATES

The principle of "sympathetic blockade" in the treatment of states of anxiety was suggested by the work of Cannon,[1] who found that the tachycardia, raised blood-pressure, increased sweating, and mobilisation of liver glycogen in some emotional states were due to overactivity of the sympathetic nervous system. This work has directed attention to the therapeutic possibilities of acetylcholine; and its administration in cases of schizophrenia[2] and the anxiety states[3] was described at the International Congress of Psychiatry in Paris in 1950.

At a meeting of the psychiatric section of the Royal Society of Medicine on April 8, Prof. J. J. López-Ibor, of Madrid, said that he regards recurrent anxiety states as part of the phasic group of mental disorders described by Kraepelin. The anxiety in these cases he believes to be neither psychogenic nor reactive, but "vital"—that is biological in origin—and he suggests that the phasic course is controlled by the diencephalon. To the various forms of anxiety state that constitute this group he gives the name of "timopathic disorders," as they are all characterised by a feeling of restlessness, dread, and apprehension—a feeling that something terrible is going to happen—which the patient refers to dangers arising within himself. Primary symptoms include cardiac dysfunction and dizziness, and there is a tendency for anxiety to be transferred to new symptoms arising in the course of the illness. The "timopathic" disorders include manic-depressive psychosis of the type in which the patient is anxious and inhibited; pure "anxiety timopathy" with "vital" anxiety; states of chronic fatigue due to nervous tension; and organic or visceral neuroses with a phasic course. López-Ibor holds that these are all "vital" or somatic in origin, and that thus they are amenable to pharmacological treatment but unresponsive to psychotherapy: but he grants psychotherapy a preventive and supportive rôle, and thinks that it may help to prevent these conditions becoming fixed and chronic. Electroconvulsive therapy he does not think suitable for the "timopathic disorders"; for the severity of the treatment is out of proportion to that of the illness, and anxiety over the convulsion and loss of consciousness is especially severe in these patients, who dread, above all, the dissolution of their personality. A freshly prepared solution of acetylcholine bromide 0·2 g. in distilled water is given intravenously, the injection taking 30–60 seconds. It is given with the patient fasting, either in the morning or in the evening, and produces fall of blood-pressure and slowing or momentary arrest of the heart. The reaction is severe, but in several hundred cases he has met with no fatality. A five-year follow-up shows cure or pronounced improvement in over 60% of cases. Patients of pyknic or athletic build do better than asthenics, and acute cases better than chronic; in obsessionals or patients with organic neuroses overt anxiety is a favourable prognostic sign. Due care must be taken in the selection of cases, both from a mental and physical standpoint.

Opening the discussion, Dr. William Sargant described work with acetylcholine bromide that has been initiated at St. Thomas's Hospital, London. He has not found that it benefits the hysteric, except at first by its suggestive effects; nor does it help patients with panic reactions who have an *immature personality* and an asthenic physique. He thinks that its chief value is in the treatment of mildly obsessional patients with severe tension states who do not respond to E.C.T. The best results, in his experience, are obtained in people of pyknic or athletic build whose anxiety is obsessional or confined to one topic. It also relieves headache or other pains associated with tension, and thought-disorder with tension—for example, inability to concentrate because of obsessional thoughts. It is now being given to outpatients in three or four treatments a week, with reduction of this number after ten or twelve weeks; and he finds that some patients are helped after the course of injections by an occasional maintenance dose. Dr. Sargant said that he wanted to investigate the treatment in order to discover the best methods of selecting cases; for to use new methods of therapy in psychiatry as a sort of universal panacea only led to their eventual discredit.

That states of chronic anxiety with tension are a real therapeutic problem to psychiatrists of all persuasions was shown by the large audience and the lively discussion. Acetylcholine therapy has a claim to serious consideration as a method of affording somatic relief to some patients; but a combined approach from the psychogenic and biological standpoints remains no less desirable than ever.

HEPATIC COMA

Mental and neurological changes, culminating in coma and death, have been recognised since ancient times as occasional features of liver disease. The widespread epidemics of infective hepatitis during the past few years have provided an opportunity for studying the relation between the central nervous system and the liver; and Walshe,[1] who has investigated 18 cases, gives an excellent picture of the disturbances. Except for coma, no single feature was common to all his cases. Definite personality changes, though they can be quite dramatic, are rare; but a short period of confusion and disorientation usually precedes loss of consciousness. The comatose patient commonly lies in a characteristic attitude, with legs crossed and hips fully flexed. Apart from dilatation of the pupils and hippus, cranial nerve disorders are rare. Symptoms of pyramidal and extrapyramidal disturbances, however, are quite common; the former include spasticity, increased knee-jerks, ankle-clonus, and extensor plantar responses, and the latter choreiform movements and athetoid postures in children and "lead-pipe" and "cogwheel" rigidity in adults; twitchings and increased myotatic irritability were present in 5 cases, but convulsions did not occur.

At necropsy the demonstrable anatomical damage to the brain is usually negligible—*œdema* and some perivascular hæmorrhage are the most usual findings—and this agrees with the clinical observation that patients who survive may recover completely. The disturbance

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[1] Cannon, W. B. Bodily Changes in Pain, Hunger, Fear and Rage. New York, 1935.

[2] Fiamberti, A. M. *Congr. int. Psychiat. Paris*, 1950 part 4, p. 59.

[3] López-Ibor, J. J. *Ibid* .p. 85.

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[1] Walshe, J. M. *Quart. J. Med.* 1951, 20, 421.

is apparently biochemical, though its character is uncertain. Hypoglycæmia might be expected to have an important rôle in determining the clinical picture of advanced hepatic necrosis. A very little surviving liver, however, can maintain a normal blood-sugar level, and in most cases of hepatic coma the blood-sugar is in the normal range. Since the liver plays an important part in detoxication, hepatic coma has sometimes been ascribed to inadequate detoxication of toxins absorbed from the small intestine. As Walshe rightly points out, however, on such a basis all patients with a portacaval shunt should pass into coma. A more attractive hypothesis, put forward by Labby,[2] is based on the fall in the serum-cholinesterase level in parenchymal liver disease. This fall, if sufficiently pronounced, could lead to accumulation of acetylcholine, which might well result in severe cerebral disturbance. On the other hand, complete destruction of serum-cholinesterase by di-isopropyl fluorophosphonate does not precipitate cerebral symptoms in cases of hepatitis, nor does raising the serum level to normal by appropriate transfusion alleviate the symptoms when present. Paper chromatography has opened the way to more detailed study of the disturbance of amino-acid metabolism in hepatic disorders. In mild cases the amino-acid pattern in body-fluids may be strikingly abnormal, even though the level of total amino-acids is normal. In more severe cases there is a pronounced increase of many of the amino-acids in the urine, plasma, and cerebrospinal fluid (C.S.F.). In a study of 15 patients in hepatic coma, Walshe found gross amino-aciduria in 8, a similar but less pronounced state in 3, and an abnormal pattern affecting principally cystine, β-amino-isobutyric acid, and γ-aminobutyric acid in 4. Plasma was examined in 5 of these cases, and C.S.F. in 3: an increased concentration and abnormal pattern of amino-acids was found in all. In the C.S.F. the most striking abnormality was an excess of glutamine. This is normally the dominant amino-acid, but in comatose patients it was not only absolutely but also relatively increased. In 2 of these fluids glutamic acid was also present.

From these findings Walshe tentatively concludes that hepatic coma results from the toxic action of amino-acids, and that the cause is inability of the injured liver to maintain the normal amino-acid balance in the plasma. The evidence for this, however, is circumstantial. Glutamine and glutamic acid are the most important of the amino-acids for cerebral metabolism,[3] but it is difficult to understand why a moderate increase of their concentration in plasma and C.S.F. should so profoundly disturb cerebral functions. Is it not at least as probable that the disturbed cerebral function accounts for the increase of these amino-acids in the C.S.F.? The pattern of the amino-acids in the C.S.F. in other forms of coma might help to settle this question; and it would be interesting to know whether coma can be produced experimentally by intravenous or intracarotid injections of these acids. The finding by Amatuzio and Nesbitt [4] of a raised blood-pyruvate in hepatic coma led them to postulate some interference in carbohydrate metabolism —possibly faulty incorporation of pyruvic acid into the Krebs cycle. The rise in pyruvate is, however, not alone responsible for the coma, since similar increases take place in many non-comatose states. If this rise in hepatic coma merely indicates disturbed hepatic carbohydrate metabolism, it throws no real light on the relation of the cerebral disturbance to that of the liver. If, on the other hand, the raised blood-pyruvate is due to impaired cerebral metabolism, how is this related to the hepatic disturbance?

The solution to the problem of this cerebral-hepatic relationship will not be found simply by demonstrating an abnormal metabolite in the plasma or C.S.F. Only when such a metabolite can be shown to result from the disturbed hepatic function, and to produce coma when introduced in similar concentration in animals and man, can the problem be regarded as solved. The further possibility that the cerebral disturbance may be due to the lack of an essential metabolite normally provided by the liver should not be overlooked.

TEACHING EVOLUTION IN THE SCHOOLS

As doctors we have been so long familiar with the theory of evolution, and use it so constantly in our day-to-day thoughts on the nature of the human body, that it is hard to realise that most young people still leave school without having heard it expounded. This is surely a handicap which could be remedied; and Prof. Julian Huxley, F.R.S., in an occasional paper,[1] puts the case strongly for teaching the principles of evolution adequately to children, so that they become a useful tool for them—an invisible framework, to use his own phrase.

Every generation in turn asks: "What are we? What sort of world do we inhabit? And in what sort of relation do we stand to that world?" The answers, in our present state of culture and with our existing mental equipment, must inevitably be partial and incomplete; but they can hardly be formulated at all, Professor Huxley insists, without some understanding of evolution as it appears throughout the universe—whether inorganic and cosmological, organic and biological, or human and social.

The first of these phases, he says,

> "concerns the transformation of lifeless matter and energy—the physical universe as a whole, the island universes within the universe, the stars within the island universes, the occasional planetary systems among the stars. The second concerns the transformations of living organisms, from bacteria and protozoa to social insects and warm-blooded vertebrates. And the third concerns the transformations of self-conscious or experience-transmitting societies, from those of submen and savages to the Renaissance and modern industrialism."

The first phase is the most extensive and the slowest; the second, which moves faster, is restricted to this planet and possibly a few others; the third is restricted, as far as we know, to one among the million or more types of organism on this planet, and is moving at an increasing rate. The basic method of the first phase is simple physical aggregation and interaction, with occasional chemical reactions added; that of the second is natural selection, with transmission of experience as an occasional subsidiary method; while that of the third is the cumulative transmission of experience alone. The results of the first phase are huge but relatively simple systems, with little variety; the results of the second, and even more those of the third, are immensely various and complex.

It is the second phase—the organic, biological phase—which on analysis supplies so much that is relevant to our general thinking. As a subject of study it has required the use of every type of scientific method—observational, experimental, quantitative, historical, theoretical. Furthermore it exemplifies the way in which scientific advance is made: the flash of intuition, the formulation of a theory, and its patient testing by the slow process of amassing evidence. Evolution is valuable in education, Professor Huxley thinks, because it provides a transition from physicochemical science to the humanities, because it throws light on man's place and destiny in Nature, and because it links the material and the mental. It shows the *universal power of living things to adapt*, the great variety of life, the trends towards improvement (most of them coming sooner or later to a stop), and the succession of one dominant type to another. Work done during the last thirty years suggests that all these aspects of life are the result of a single basic property of living matter: its not-quite-perfect capacity for self-copying. The genes of the hereditary constitution, if they were fixed (and they are nearly fixed), could produce permutations indefinitely, but nothing original. As it is, the copy is occasionally not identical with the original: a gene mutates, and the mutation confers some degree of advantage or disadvantage on its possessor. The effects are differential survival and differential multiplication, and hence every kind of evolutionary change.

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[2] Labby, D. Conference on Liver Injury: Transactions of the 5th meeting. New York, 1946; p. 120.
[3] Weil-Malherbe, H. *Biochem. J.* 1936, 30, 665.
[4] Amatuzio, D., Nesbitt, S. *J. clin. Invest.* 1950, 29, 1486.

[1] Evolution and Education. No. 6, published by the British Social Biology Council. 1951. Pp. 16. 1s.

Threading the maze of their opportunities, organisms often take an evolutionary turning which can bring them only to a dead end of development. Thus—fortunately for us—insects and land arthropods breathe by air tubes, more efficient than lungs if the size of the organism is small but becoming rapidly less efficient as size increases. A spider the size of a mouse is feasible, but one the size of a rat is out of the question. By limiting their total size insects have also limited the size of their brains. Their evolution has thus presented problems in engineering which should fascinate the young. As long as man remains in existence, no other group can hope to oust him from his position of dominance; for as soon as he recognised the threatened change he would use his superior brain to counter it.

These ideas should be part of a child's grounding in science, because they will help him to unify and integrate what he is taught. In schools, at present, human physiology is seldom related to comparative physiology or to evolution; and natural history deals only with the contemporary scene, not with the evolutionary history of plants and animals. Our policy, Professor Huxley says, should be clear: to insist that biological subjects should rank equally with physicochemical subjects in the school science curriculum, and that they should be treated whenever possible from the evolutionary angle.

NERVOUS CONTROL OF SWEATING

Kuno's work[1] has shown that there are two main types of sweating: thermal, and mental or emotional. Thermal sweating occurs in response to heating of the body and is greatest on the forehead, dorsum of the hand, and chest and neck. Mental sweating is greatest on the palms and soles, but also occurs in the axilla and on the forehead. Both types are controlled by the central nervous system, thermal sweating from the temperature-regulating centre in the anterior portion of the hypothalamus, and mental sweating from centres at different levels up to the cerebral cortex. The nerve-fibres supplying sweat-glands are distributed via the sympathetic ganglia; and the final distribution of the postganglionic fibres is mediated by the sensory nerves to the skin.[2] Thus, anatomically the nerve-fibres to sweat-glands are sympathetic; but functionally they behave as if they belonged to the parasympathetic system. For example, the activity of sweat-glands is stimulated by acetylcholine and pilocarpine, and inhibited by atropine; and Dale and Feldberg[3] have explained this anomaly by showing that the nerve-fibres which excite the sweat-glands are cholinergic (i.e., they liberate acetylcholine as chemical transmitter), whereas nearly all other sympathetic nerve-fibres are adrenergic (i.e., they liberate adrenaline, and noradrenaline, as transmitter).

Chalmers and Keele[4] have recently tried to find out whether the facts known about chemical transmission to sweat-glands could help explain the excessive secretion in hyperidrosis. They reasoned that the sweat-glands of the palms and soles might be hypersensitive to acetylcholine, in the same way that the digital arteries and the arteries of the palmar arch are hypersensitive to cold in Raynaud's syndrome.[5] In hyperidrotic patients they measured the sensitivity of the affected sweat-glands by recording the responses to different concentrations of acetylcholine injected locally; sweat secretion was measured by the iodine-starch paper method of Randall.[6] In order to test the response of the palmar sweat-glands it was necessary first to anæsthetise the median nerve at the wrist with procaine. Chalmers and Keele found that there was no significant difference in the sensitivity of the palmar sweat-glands to acetylcholine between 8 normal people and 6 with hyperidrosis; so they conclude that the excessive secretion of sweat in this condition is not due to hypersensitivity of the sweat-glands to the chemical transmitter. They found no evidence that cholinesterase activity was reduced; so the excessive sweating of hyperidrosis must be due to increased release of acetylcholine at the postganglionic nerve-endings. This increased release is most probably due to increased central nervous activity; and it is interesting that in some patients with essential hyperidrosis there is also peripheral vasoconstriction, probably central in origin but mediated via an adrenergic nerve pathway.

Chalmers and Keele[7] have also investigated the possibility that the nerve-supply to some sweat-glands might be adrenergic in man. They confirmed the findings of Haimovici[8] and Sonnenschein et al.[9] that in man sweat-glands (in forearm and palm) secrete in response to locally injected adrenaline and noradrenaline. They showed, however, that the introduction locally of adrenaline antagonists such as tolazoline ('Priscol') did not inhibit thermal or mental sweating, even when these were applied in high enough concentrations to abolish the response to injected adrenaline. Local application of atropine always abolished sweating in both forearm and palm. In this connection Shelley[10] has found that the apocrine sweat-glands of the axilla (the other glands in the forearm and palm are termed eccrine) are stimulated by adrenaline and noradrenaline and not by acetylcholine, and that their physiological activity is inhibited by adrenaline antagonists and not by atropine. This work suggests that the nerve-supply to apocrine sweat-glands in man is adrenergic in nature.

The excessive sweating of essential hyperidrosis can be controlled by atropine, which blocks the action of acetylcholine; but the doses required also inhibit salivary secretion, and may cause some disturbance of accommodation. Grimson et al.[11] have tried another acetylcholine inhibitor—β-diethylaminoethyl-xanthine-9-carboxylate methobromide ('Banthine') in the treatment of hyperidrosis, but it does not appear to be much superior to atropine. Chalmers and Keele[4] have tested the ganglion-blocking agents, pentamethonium and hexamethonium bromide, in 6 patients with essential hyperidrosis. The average dose was 250 mg. thrice daily by mouth, and in 4 of the patients the symptom was satisfactorily controlled by these drugs. Paton and Zaimis[12] have shown that these methonium compounds block transmission through autonomic ganglia by rendering the ganglion cells insensitive to the acetylcholine liberated at the preganglionic nerve-endings. Finally, where hyperidrosis arises in the apocrine glands of the axilla—and if the nerve-supply to these glands is truly adrenergic—secretion might be inhibited by such drugs as tolazoline, dihydroergotamine, and dihydroergocornine.

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1. Kuno, Y. The Physiology of Human Perspiration. London, 1934.
2. Woollard, H. H., Phillips, R. *J. Anat.* 1932, 67, 18.
3. Dale, H. H., Feldberg, W. *J. Physiol.* 1934, 82, 121.
4. Chalmers, T. M., Keele, C. A. *Brit. J. Derm.* 1952, 64, 43.
5. Lewis, T. Vascular Disorders of the Limbs. London, 1936.
6. Randall, W. C. *Amer. J. Physiol.* 1946, 147, 391.
7. Chalmers, T. M., Keele, C. A. *J. Physiol.* 1951, 114, 510.
8. Haimovici, H. *J. appl. Physiol.* 1950, 2, 512.
9. Sonnenschein, R. R., Kobrin, H., Grossman, M. I. *Amer. J. Physiol.* 1949, 159, 591.
10. Shelley, W. B. *J. invest. Derm.* 1951, 17, 255.
11. Grimson, K. S., Lyons, C. K., Watkins, W. T., Callaway, J. L. *J. Amer. med. Ass.* 1950, 143, 1331.
12. Paton, W. D. M., Zaimis, E. J. *Brit. J. Pharmacol.* 1951, 6, 155.

Special Articles

A RECOVERY WARD
ITS PLANNING AND USE

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THOUGH some hospitals in this country have wards set aside for patients recovering from operation, little seems to have been written on their scope, situation, or design. The American literature is fuller, but still small considering that the recovery ward, in some form or other, appears to be more widely used in the United States.

In 1942 a postanæsthesia room was opened in St. Mary's Hospital, Rochester, Minnesota. One bed was available for each operating-room, and the department was open from 9 A.M. to 5 P.M. Patients were never returned to their own bed until they were awake, and both male and female patients were accommodated in the same room. The number of patients admitted to the P.A.R. rose from 2071 in 1942 to 3427 in 1945 (Mayo Clinic 1945, 1948).

In 1948 the room was staffed with two graduate nurses and one orderly. Each bed was arranged so that it could be seen from any part of the room. The patient was placed with his head towards the foot of the bed. The length of stay of the patient in the P.A.R. was about the same as his stay in the operating-room. During the critical postanæsthesia period one nurse did the work which usually requires the services of three nurses (McQuillen 1948).

Similar facilities were introduced in three hospitals in Rochester, and in 1949–50 16,985 patients passed through these rooms. Further extensions to this service were under way in 1951 (Mayo Clinic 1951).

The Anæsthesia Commission of the Philadelphia County Medical Society observed many errors in resuscitation, "foremost among these being inefficient methods of maintaining respiratory function when it was depressed or paralysed. Inadequate nursing care coupled with respiratory obstruction in the postoperative period occurred in 95 cases" from a total of 307 fatal cases. The commission said that "the need for post-operative observation rooms under trained personnel and under the direction of the anesthesia service was obvious," and thought that "there should be more post-operative anesthesia recovery rooms, where care can be given the patient immediately after anesthesia. We find that there is a considerable incidence of respiratory obstruction in the immediate post-operative period" (Ruth et al. 1947).

In 1948 Noble described a small unit of 5 beds in two rooms, on the same floor as the operating-theatres. During four months 277 patients, or 60% of all surgical cases, passed through this unit. Of this number, despite routine post-anæsthetic care, "which undoubtedly prevented considerable trouble, approximately 8% had complicating episodes during recovery" (Noble 1948).

A report on 35,000 recovery-room cases handled in the previous seven years by a single group of anæsthetists working in two hospitals in the District of Columbia says that "since the advent of the recovery room in these hospitals such serious complications [as respiratory obstruction] have been prevented in all cases in which the recovery room was utilised. Unavoidable sequelæ to anæsthesia such as respiratory depression or circulatory depression, when they have occurred, have been detected sooner and more properly managed" (Lowenthal and Russell 1951).

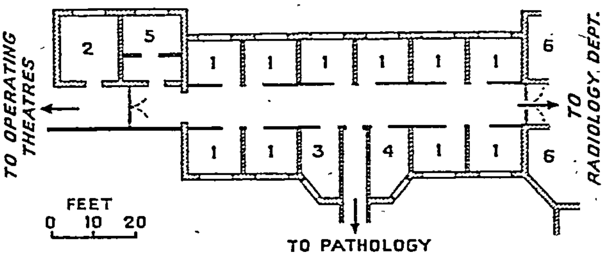
Anderson (1951) includes in his discussion of the supervised emergence of the anæsthetised patient plans and diagrams of suggested structural lay-outs. All allow for only a limited number of beds.

A BRITISH RECOVERY WARD

At the Plastic Surgery and Jaw Injury Centre, Queen Victoria Hospital, East Grinstead, before February, 1946, the recently anæsthetised patient was returned to his own bed. This practice gave rise to a number of incidents, and there had been two deaths. The local geography gave rise to difficulties, for the single-storey hutted wards were at some distance from the operating-theatres: indeed the distance between bed and operating-table was in one case over 400 yards. Each ward was equipped with oxygen under pressure, a suction apparatus and a carefully planned resuscitation tray carrying injection materials and drugs, endotracheal tubes, gag, tongue clips, tongue spatulæ, sponge-holders, box-wood wedges, and airways of various types. Nevertheless, incidents occurred, especially in patients undergoing extensive facial repairs.

Through the generosity of the British American War Relief Fund, plans had been made since 1944 for a new surgical centre. This, however, would further increase the distance between bed and operating-table, and the anæsthetic staff of the unit urged the inclusion of a recovery ward in the new scheme. This was agreed on the basis of 10 single-bed rooms attached directly to the operating suite (see figure). (The operative turnover at that time was 1720 per year and steadily rising.)

In close relationship to this ward was the pathological laboratory with its blood bank, the X-ray department, and the dispensary. Each room of the ward had an outer wall and an inner glassed wall, which adjoined a central corridor (see figure). At the centre of one side of this central corridor were a kitchen, a dressing-room equipped with sterilisers, and storage space for all resuscitative drugs and equipment. Also included in the plan was a sluice-room and a large linen-storage room, to accommodate the large stocks of bed-linen required to care for a rapid bed turnover.



Plan of the recovery ward

1. Recovery rooms
2. Linen room
3. Dressing-room
4. Kitchen
5. Sluice room
6. Dispensary

Each room was fitted with a wash-basin and a fixed unit giving piped oxygen with built-in flow-meter, piped suction, bell, and various electrical tappings for bedside lamps, electric blankets, &c. The 10 beds in the department were equipped with 'Sorbo' mattresses and large castors, 2 being of the Lawson Tait variety. Doors, both of the rooms and of the corridor, were wide enough to allow a bed to pass through easily. In an emergency each room could, for a short period, take 2 hospital beds or 3 cots.

The ward was placed in the general charge of the anæsthetic department, and at no time has any surgeon, without prior consultation, had the use of a bed other than for the recovering patient. Our surgical colleagues have helped us enormously in our task by the restraint of their requests.

During the operating sessions the sister in charge of the ward pays frequent visits to the adjoining operating suite to discuss the management of the cases with the surgeon and anæsthetists. If any patient is transferred directly from operating-table to bed in the theatre, the sister is present. The rest of the staffing was at first frankly experimental. Originally in addition to the sister-in-charge there were two trained staff-nurses and one assistant nurse. This staff has grown, and now, besides the sister-in-charge, the day staff consists of four State-registered nurses, and two male orderlies.* The night staff consists of a State-registered nurse and an assistant nurse. If more staff is needed in an emergency, nurses have always been provided.

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* It is interesting to note that the Whitley Council has rejected a request by the hospital authorities for recognition of the sister-in-charge as a departmental sister.

The following equipment was supplied to the ward:

Electric blankets for bed-warming; all necessary equipment for transfusion, infusion, and all types of intravenous and other injections; oxygen administration equipment (the B.L.B. mask or a variant is almost universally used); suction catheters in various sizes; tongue clips, gags, oral props, sponge-holders, and endotracheal and short nasal tubes. For special types of surgery there is special equipment—e.g., a pair of wire-cutters is at the bedside of every case of fractured jaw returning from the operating-theatre with the jaws wired together. After recovering consciousness these patients will require special feeding-cups. Children after operation for cleft lip or palate should have the arms splinted for some hours. Patients who have had impacted wisdom teeth removed will have ice-packs applied continuously for six hours.

All these and other special treatments require their own equipment, which now need not be available in every ward in the hospital, but only in the recovery ward. So here emerges one of the advantages of such a ward—over-all economy of equipment.

HOW THE WARD IS USED

After his operation the patient is taken by theatre trolley to his room in the recovery ward. There he is transferred to the warmed bed, the theatre technician or orderly helping the recovery-ward staff. At the same time the technician or orderly conveys to the ward staff verbal instructions additional or supplementary to those given directly by anæsthetist or surgeon to the sister on one of her frequent visits to the theatre. These instructions include special nursing instructions or special points to be watched for in the recovery period.

The more experienced the staff becomes, the fewer instructions will be necessary. Before leaving the patient the theatre nurse gives the nurse-in-charge a written note confirming the operation performed and any special details of dressings, drainage tubes, &c., applied at operation. The patient is not left unattended until all reflexes have returned and any artificial airway has been removed. At this point the care may become intermittent, but a close watch is kept either directly or through a "port-hole" in the glass wall of the room. We have found that patients treated in this way, and left in a closely watched peace, will require little postoperative sedation, and will sleep, though easily roused, for many hours. During the postoperative period any treatment required—e.g., antibiotic therapy—is inaugurated or continued as necessary, the appropriate records being made in the ward treatment book. Sedatives are given as required and as ordered. This item, particularly in patients with facial fractures, requires close control. We have seen fatalities and near-fatalities from too early and overenthusiastic morphinisation; we have also seen the results of surgery destroyed in moments because the administration of morphine was timid or too long delayed.

Most patients stay in this ward until 9 A.M. on the morning after their operation. Throughout the twenty-four hours one or more members of the anæsthetic department are on call to deal with any emergency or point requiring advice or clarification. They will initiate transfusion, and advise on oxygen therapy, problems of feeding, and medication. They will be able to observe those occasional and often fleeting phenomena such as "thiopentone twitch"; the short period of nystagmus following emergence from barbiturate anæsthesia; the odd acts that some patients perform when emerging from anæsthesia, and so on. If a patient is gravely ill, his return to the ward is delayed until he is fit for transfer.

Before the patient leaves the ward on the morning after operation, the recovery ward produces a short note on the operation and subsequent treatment for the information of the patient's own ward staff. Therapy to be continued will be noted. Any extraordinary points of note will be recorded.

Each day the ward sister completes a record of each patient—including name, age, ward to which returned, operation, length of stay in the recovery ward, and any special notes on treatment, on postoperative sequelæ (e.g., vomiting and its nature and duration), on any cough, sore throats or headache, and on urinary function.

HOW MANY BEDS PER THEATRE?

Our ward has 10 beds in 10 rooms, but usually there are more than 10 operations on any normal work day. To avoid the direct passage of any patient to his own bed, thus short-circuiting the recovery ward, three expedients have been adopted:

(1) The inclusion of a second bed in one or more rooms; or the inclusion of two or even three cots for infants, in one room. Contrary, apparently, to the practice in some American clinics, segregation of the sexes is practised.

(2) The earlier return of some patients to their own wards. No such return is ever carried out except under the direct selection of the anæsthetist responsible for the particular case.

(3) The acceptance of one or two additional and suitably screened beds in the corridor itself. The patients so treated are always those provisionally selected for early return to their own wards. In these cases the patient's own bed is often obtained from his own ward.

One or more of these expedients is used on about four days in the week, but we do not regard them as satisfactory. The anæsthetic staff of the Mayo Clinic find 1 recovery bed per operating-theatre is adequate. Our experience over the last six years, is that, with the use to which we put our ward, 2 beds per theatre is *in*adequate.

The number of patients passing through the ward each year since it was opened is shown in the accompanying table. Patients who stayed in the ward for more than twenty-four hours are not counted more than once.

ANNUAL USE OF RECOVERY WARD AT THE QUEEN VICTORIA HOSPITAL, EAST GRINSTEAD

—	No. of operations	No. of patients accommodated in R.W.
1946 (from February) ..	1882	1478
1947	2054	1687
1948	2396	1995
1949	2771	2387
1950	3160	2708
1951	3589	2809
Total	15,852	13,064

THREE POINTS OF VIEW

The Anæsthetist

From the viewpoint of the anæsthetic department the recovery ward has been nothing but a blessing. No patients have died in the immediate postoperative period. With but few exceptions respiratory difficulties have been met only in those types of cases in which they might have been expected. These have included patients with jaw injury or facial fractures; patients who have sustained damage to the floor of the mouth; patients who have to maintain abnormal positions postoperatively—e.g., the head fixed with marked lateral deviation and flexion following the attachment of an acromiothoracic tube pedicle to the nose. Wherever difficulties or near-fatalities have occurred we have been able to institute immediate treatment.

With the introduction of controlled hypotension in surgery, the recovery ward became, to our mind, essential. Changes of posture after operation have to be so carefully controlled that we have felt that transport to a ward at a distance from the operating-theatre and the anæsthetist would be a bar, or at least a serious deterrent to the use of this procedure. To date about 10% of our 12,000 cases have been given controlled hypotension, and few, if any, have been returned to their own ward before the morning after operation.

The Nurse

When the ward was started the nurses feared that they would lose valuable experience in postoperative nursing care in this branch of surgery. After a year we asked their opinion again. The result was interesting. Nurses who had worked on wards both before and after the recovery ward was started found that they would be unwilling once more to undergo the strain of the hazards of the postoperative care they had practised. Nurses who had worked on the recovery ward found that they secured a confidence in the handling of these hazards. Furthermore they saw the immediate postoperative results of virtually all the operations performed in the hospital. In a short period they would see a cross-section of all procedures carried out in the Plastic Surgery Unit.

The addition of this ward has not increased the total number of nurses of the hospital. Indeed the sister of the largest ward estimates that return of immediate postoperative nursing to her charge would oblige her to ask for five more nurses—i.e., the present number of staff in the recovery ward. In this hospital there are, besides this large surgical ward of 49 beds, two 30-bed wards; one 18-bed ward; two 12-cot wards, and 50 convalescent beds. Thus there may well have been a true reduction in the number of nurses required to staff the hospital.

We realise that the inclusion of a recovery ward in a general hospital which is also a nurses' training-school could well give rise to difficulties in ensuring that every nurse in her training would spend a period in the recovery ward, while ensuring that there was always an adequate cadre of experienced staff to maintain the ward at its peak of efficiency. Surely, however, such a problem should be capable of solution.

The Patient

The benefits to the patients have more than justified the expense of including a recovery ward in the original plans. Postoperative anxiety has decreased. There have been no deaths during the period. So strongly do we believe in the advantages of such a ward that we would welcome the opportunity of observing an adequate recovery ward at work in a general hospital. Difficulties occur in all types of anæsthetic service—often in those patients for whom one would predict an uneventful recovery period. For this reason we believe that all patients should pass through a recovery ward after operation. Selection of the patients before their recovery may well be uncertain. It is *not* always possible to determine which patient is going to give trouble. We would urge that all—or none—of the patients pass through a recovery ward. Thus there can be no regrets, or recriminations, for incorrect selection.

THE DESIGN FOR A RECOVERY UNIT

Combined Preoperative and Postoperative Unit

This would consist of two equal blocks connected by central offices consisting of sterilising-room, dressing-room, linen store-room, linen-sorting room, sluice-room and kitchen. Each block would contain a number of beds equal to the greatest number of operations performed under general anæsthesia in one day. Failing this ideal the number of beds would equal the average number of cases operated upon daily. For example, 3650 operations per year under general anæsthesia would require, a minimum of 10 beds in each block.

On Sunday afternoon and evening patients for Monday surgery would be admitted and prepared for anæsthesia by the anæsthetic department. After surgery on Monday these patients would return to the beds in block A. During Monday afternoon the patients for Tuesday surgery would be admitted to block B for preparation. On Tuesday morning the patients from block A would return to their own wards. The staffing problem would be solved thus. On Monday block A staff would be at the level of one nurse to 2 patients, and block B one nurse to 5–7 patients. Tuesday, the reverse. For administrative purposes the staff of the two blocks would be considered as a single unit. The night staff of both blocks would be equal in size.

Postoperative Unit

Ideally the number of beds in the unit should equal the largest operation list done in the hospital; at second best, it should equal the average number of daily operations. But even a small number of beds can serve a most useful purpose. Anderson (1951) suggests that patients may be cared for in specially designed postanæsthetic stretchers, as an alternative to bed care. This assumes that the postanæsthetic patient is truly a migrant.

In this unit we have found that with a turnover of about 3500 operations a year, 10 beds are insufficient, but 15 beds would cover our present needs satisfactorily. As the operating turnover shows a persistent tendency to rise by 10–15% per annum, difficulties are likely to arise in the near future. We have asked that extensions to the unit should be included in the annual estimates of the hospital.

Some Desiderata

The following points, we feel, are of prime importance in planning a recovery department.

1. All patients undergoing general anæsthesia should pass through a recovery ward. Less work is involved in keeping the patients until the morning after operation than in maintaining a flow throughout the day, and the recovery of the patient is less eventful.
2. The number of beds should at least equal the average number of daily operations.
3. Each bed or pair of beds should be sound-insulated from the rest of the ward.
4. The ward should *not* contain a bathroom. It is sometimes difficult to resist a call for borrowing a bed. The absence of a bathroom makes a room less desirable, and the request easier to resist.
5. A "bed park" should be included. A reserve of assembled beds should be permanently available for use in emergency.
6. All beds should have removable head-pieces. We feel that this should apply to all hospital beds anyway.
7. Suction and oxygen should be beside every bed—preferably piped.
8. Each room should be shielded from the direct sun, yet light and airy. Each room should be capable of being darkened. The whole ward should be maintained at an even temperature.
9. The ward should be an appendage of the operating suite.
10. The ward should be the responsibility of an anæsthetic department.
11. The nursing staff should never be changed en bloc. Some experienced nurse must remain when staff is changed.

CONCLUSIONS

A few hospitals in this country and in America have started recovery wards. Those who have worked in such wards are unanimous in their appreciation of the service which they give to the patient.

Having a recovery ward does not mean that more nurses are needed: indeed it may reduce the number the hospital requires. Equipment is undoubtedly saved, particularly where pipe-lines for suction and oxygen are provided.

The capital expense of such a unit must be heavy, but the ultimate gain, primarily to the patient by virtue of the greater safety of his operation, and secondly to the hospital balance-sheet, is a stimulus to planning such departments.

At the moment a team appointed by the Nuffield Provincial Hospitals Trust is inquiring into the ideal lay-out for a recovery ward.

A set formula for the size of such a ward will be difficult, if not impossible, to find. Any plans made should allow for: (1) the care of *all* patients undergoing surgery with general anæsthesia; (2) close contact with other services—e.g., radiological and pathology departments; (3) a high level of staffing, with a permanent core of experience; (4) general supervision by the anæsthetic department; and (5) expansion.

Many names have been given to these units by different authorities. Might we plead for the use of the simple and descriptive term—recovery ward ?

Our thanks are due to our surgical colleagues for their support of this experiment; and to Dr. A. A. Mason for the illustration. We, and all our patients, owe a great debt to the two sisters who have been in charge of the ward for dealing so generously with our requests and so understandingly with our experiments and whims.

REFERENCES

Anderson, C. D. (1951) *Anesthesiology*, 12, 604.
Lowenthal, P., Russell, A. S. (1951) *Ibid*, p. 470.
McQuillen, F. A. (1948) *J. Amer. Ass. Nurse Anesthetists*, 16, 20.
Mayo Clinic Section of Anesthesiology (1945) *Proc. Mayo Clin.* 20, 292.
— (1948) *Ibid*, 23, 301.
— (1951) *Ibid*, 26, 290.
Noble, A. B. (1948) *Hosp. Progr.* 29, 272, 289.
Ruth, H. S., Haugen, F. P., Grove, D. D. (1947) *J. Amer. med. Ass.* 35, 881.

IMPERIAL CANCER RESEARCH FUND

THE annual general meeting of the Fund, held last Tuesday at the Royal College of Surgeons, with Prof. H. R. Dean in the chair, received the annual report for 1951–52 from the director, Dr. James Craigie, F.R.S.

Carcinogenesis.—Feeding experiments have been initiated by Mr. H. G. Crabtree to test the hypothesis that *p*-aminobenzoic acid (and possibly folic acid) may be a critical inhibiting factor in the genesis of liver tumours by azo-carcinogens. Results so far obtained are in conformity with this hypothesis.

Hormones.—Mr. P. C. Williams has continued the comparative study of the endocrine functions of the inbred strains of mice maintained in the Fund's laboratories. The investigation of possible neural control of adenohypophyseal function, by the late Dr. E. Vazquez-Lopez and Mr. Williams, reached a stage when a preliminary communication could be given at a Ciba conference last summer.

Ascites Tumours.—It had been found that survival of tumours in the frozen state could be accounted for by survival of a few cells which happened to be in a highly resistant state at the time of freezing. Ascites tumours provide a rich source of cells capable of assuming this resistant state and during the past year these tumours and various associated problems have been investigated by Dr. Craigie with the collaboration of Miss P. E. Lind, Miss M. Hayward, PH.D., and Dr. A. M. Begg.

Low-temperature Preservation of Tumours.—The use of frozen stocks has greatly simplified much of the experimental work, not only by eliminating the necessity of continued maintenance by serial passage but by providing easier control of dosage where this is critical. Recent tests of tumours stored in the frozen state for over two years show an activity comparable with fresh tumour fragments.

Mammary Cancer.—Dr. B. D. Pullinger has continued her studies of mouse mammary tumours at the Research Department, Royal Cancer Hospital, Glasgow. Since 1944 a pure line strain of mice has been bred having a mammary-cancer incidence of less than 2%. This substrain was derived by cross-suckling—to free it from Bittner's milk agent—from the R III strain, which previously had an incidence of about 80% of mammary cancer. Non-malignant adenomatous nodular proliferations have been found in about 20% of breeders over one year old, besides squamous and adenoacanthomatous nodules in another 20%. The cause is unknown. On account of their greater variety and later age-incidence the tumours resemble human breast cancer more closely than do those due to Bittner's agent.

Clinicopathological Research.—A research laboratory has been established in the pathological department at the Royal College of Surgeons, under the general direction of Prof. Geoffrey Hadfield. It was decided that the investigation should in the first place be restricted to cancer of the breast and prostate, and arrangements have been made with the Westminster Hospital, with St. Peter's Hospital and the Institute of Urology, and with the surgical unit of St. Bartholomew's Hospital. The collaboration of Dr. E. F. Scowen (St. Bartholomew's) has been secured. The staff consists of two pathologists, Dr. L. M. Franks and Dr. J. Stretton Young, with a senior and a junior technician, and Dr. George Lumb (Westminster) is an active member of the team.

This 49th annual report carries a historical supplement entitled Fifty Years of Cancer Research.

Medical Conferences

FATIGUE

ERGONOMICS RESEARCH SOCIETY'S SYMPOSIUM

A SYMPOSIUM on fatigue, organised by the Ergonomics Research Society, was held at the College of Aeronautics, Cranfield, on March 24–27. The programme covered most aspects of this ill-understood subject. The majority of speakers did not attempt to define fatigue, but Sir FREDERIC BARTLETT, F.R.S., who opened the symposium, proposed the following definition:

> "Fatigue is a term used to cover all those determinable changes in the expression of an activity which can be traced to the continuing exercise of that activity under its normal operational conditions, and which can be shown to lead, either immediately or after delay, to deterioration in the expression of that activity, or, more simply, to results within the activity that are not wanted."

Sir Frederic considered that abnormal conditions were not particularly suitable for the experimental investigation of fatigue. If the operator is submitted to excessive heat or cold, or intense noise, vibration, or buffeting, great heights, or great depths, the complications produced by such abnormal conditions, although they may accentuate "fatigue," make it difficult to evaluate the results. This is a point of considerable importance, as many of the investigations described in the course of the symposium involved studies under just such abnormal conditions.

It was clear both from his paper and that of other speakers that it is unlikely that any one definition will cover what is meant by fatigue. In fact, it is possible that this word, like "shock" and possibly "stress," has outlived its usefulness for scientific purposes. There are clearly many types of fatigue—mental and physical, acute and chronic—and it is all too easy for a valid description of one type to be confused with research in what amounts to an entirely different field. The word "fatigue" may therefore possibly be confined to conditions included within Sir Frederic's definition, and the word "stress" used for the abnormal conditions such as those mentioned above.

CRITERIA

Sir Frederic suggested three criteria of fatigue which deserved further study. Experimental study of muscular fatigue, using, for example, an ergograph, showed that sooner or later irregularities in the succession of events began to appear. These irregularities appeared without any awareness at all on the part of the operator. There was considerable evidence to show that the earliest and the most delicate criterion of the change in activity due to the continuance of that activity was an increasing irregularity of the successive items comprising the performance. It may well be that a similar increasing irregularity occurs in mental fatigue, although it is more difficult to measure such irregularities objectively.

The second criterion is disintegration of the field of display, with the consequence that the right actions are done at the wrong time and some actions may be omitted altogether. The field of display consists of all the items in the field concerned with the task in hand. Some of these items are more directly concerned with the task than others, which might be called outliers. The last are the ones which will be either ignored or emphasised at the expense of the central features as fatigue develops. These account for the "lapses" of behaviour which commonly mark advancing fatigue of body or mind. Some experimental work on this aspect of fatigue was described by D. B. BROADBENT.

The third criterion of fatigue concerns the subjective effects which are a common feature of a long-sustained activity. Localised discomforts, aches, and pains, and awareness of uncomfortable posture are amongst the many and varied symptoms, which may well be related to the irregular timing and performance and the disintegrating display field which comprise the first two criteria. The disintegrating field may paradoxically extend the field itself, so that many elements of the total situation, external and internal, which did not command response in the unfatigued state now do so. That is to say, fatigue involves a progressive widening of the field from which selection is made, with a consequent loss of direction. It was pointed out by Bartlett that it was a characteristic of all these manifestations that they fluctuate, and what he described as a " dogged fortitude " would often carry a man through to a second wind.

ANATOMY AND FATIGUE

Some of these points were illustrated by papers with a different background. H. D. Darcus, for example, described changes in muscular activity. He quoted the work of Knowlton et al.[1] in support of his contention that when a constant output of muscular effort is maintained there is a progressive increase in the muscular activity to produce the same amount of work, and this increase is due to an increasing contraction of individual muscles and to a recruitment of other muscles. As the muscle work progresses the activities cease to be smooth. Motor units, instead of contracting out of phase, tend to contract in groups. In alternating movements the period of activity also increases, so that muscles never relax completely. An operation demanding flexion of the middle finger will not involve movements of the other fingers initially, but as fatigue progresses the other fingers start to move involuntarily although they appear to achieve no useful purpose, and activity may be recorded from remote parts of the body. Finally, the muscles involved in the movement may fail, and in order to maintain output efforts are made to get the same results by using other muscles which may not be adapted to the particular work. These points, of course, are concerned with the first criterion of fatigue discussed by Sir Frederic Bartlett.

It is clear, that in this aspect of the study of fatigue there is real advance in the correlation of physiological and psychological observation.

J. W. T. Redfearn described his investigations of finger tremor and demonstrated three main frequency components at about 30 cycles per second, 6–10 cycles per second, and 2–4 cycles per second, the highest of these frequencies being the natural frequency of the finger. The exercising of muscles which act on the finger increases tremor at the low frequencies. Severe general muscular exertion, not necessarily involving the muscles acting on the finger, also increased tremor in the 6–10 cycles per second band. On the other hand, sleep deprivation did not appear to affect tremor at all.

PHYSIOLOGICAL BACKGROUND

A. Hemingway pointed out that muscle contraction can only be sustained if blood-flow through the muscle is maintained. A maximal contraction exerts such a tension on the blood-vessels that blood-flow through the muscle may be completely suppressed. This will prove a limiting factor in any sustained static work. On the other hand, provided that the contraction is not maximal, the muscle tension may not be sufficient to cut off the blood-flow; so there may be an increased blood-flow not only after contraction has ceased but during the contraction itself. In general, therefore, rhythmic work—alternating contraction and relaxation of muscle-groups—is more easily maintained for long periods because an adequate circulation will continue through the active muscles.

Analysed solely in terms of neuromuscular activity, the failure of a muscle to continue to develop tension at the original level may be due to failure of the fibres themselves to develop tension, or of the nerve-impulses to reach and affect the muscle-fibres. Failure in the neural mechanisms might be due to impairment of conduction in nerve-fibres, or of synaptic transmission, or of muscle end-plates. It has been shown that, with continuous use, impairment can occur in all these situations despite the classical view that the muscle end-plate is the site of neuromuscular fatigue.

The transmission of nerve-impulses or the development of tension in muscle-fibres presumably entails a release of energy and the subsequent restoration of the system responsible for its release—a process which may depend on local resynthesis or the use of stored material. In the long run, continued restoration is likely to require the arrival of fresh material and the removal of products of activity.

The time of onset of fatigue at a particular rate of working may be determined, therefore, by the rate of transport of materials to or from the site of activity, and the maintenance of a store of material over a period will depend on supplementation.

In some instances the activity itself may have " side-effects " which prevent the full use of transport mechanisms by the working tissue. For instance, the circulatory adjustments necessary for temperature regulation during prolonged and severe muscular effort in a warm environment take a larger proportion of the available cardiac output than when the effort is made in a cool environment. Or, for another example, two forms of muscular activity may be equal in metabolic cost, but one favours the venous return to the heart while the other, owing to sustained muscular contraction, hinders it.

FACTORS IN ONSET OF FATIGUE

H. R. Noltie described his work on the effect of preliminary warming or limbering up in exercise performance. His results suggested that the size of the oxygen debt was decreased by preliminary limbering up, and this may delay the onset of fatigue in so far as it is due to oxygen lack.

NEGATIVE AND POSITIVE WORK

E. Asmussen (Copenhagen) discussed the cost of negative and positive work. Negative work means muscle contraction, together with lengthening or stretching of the muscle: walking downstairs or lowering weights are examples. Asmussen has carried out experiments measuring the oxygen consumption at various levels of positive and negative work. Even at very high rates of negative work the oxygen consumption is low, and it may well be that this important fact could be taken into account by designers of machinery and equipment requiring muscular work for their operation.

WORK EVALUATION

E. H. Christensen (Stockholm) described experiments to determine whether the tasks performed in a steel mill were too exhausting. There were many difficulties in using exact physiological methods to determine caloric expenditure, and Christensen therefore relied on a number of simpler measurements, including heart-rate, rectal temperature, skin-temperature, and, in a number of cases, oxygen consumption using the Douglas bag technique. He showed from previous work that in any individual, provided that the environmental temperature is not excessively high, oxygen consumption is directly correlated with heart-rate and also with rectal temperature, and that one may therefore derive from measurements of rectal temperature and heart-rate an approximate level of energy expenditure.

Christensen discussed the general applications of his work in industry from the point of view of what should be physiological criteria for sustained work. He proposed that half the maximum capacity should be the limit for tolerable sustained work. Maximum capacity should be defined as the maximal oxygen consumption of which the individual is capable. The maximal oxygen consumption has been previously shown by Kjellberg et al.[2] to be directly related to the total hæmoglobin content or hæmoglobin mass, and this relationship holds good regardless of age and sex.[3]

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[1] Knowlton, G. C., Bennett, R. L., McClure, R. *Arch. phys. Med.* 1951, 32, 648.

These very important concepts put forward by Christensen aroused considerable discussion, and it is clear that more work is needed by physiologists before exact physiological limits of work can be laid down with assurance. However, some of the limits given by Christensen might be accepted provisionally, and work which exceeds such limits should be prohibited. There are obviously many important consequences of such ideas. There is, for example, the social problem of how much of a man's total energy expenditure should legitimately be demanded in his occupation. Should he be left so exhausted at the end of his work that it is only by complete rest during the remainder of the day that he is able to resume work the next day? Observations that have been made in factories show that individuals engaged in physically light work will spend their free time in active recreation, whereas the heavy worker often goes home and sits in a chair or may even go to bed.

FATIGUE ALLOWANCE

In opening the discussion on fatigue allowance, T. U. MATTHEW briefly reviewed the early history of factory practice, referring to the pioneer work by F. W. Taylor[4] and F. B. Gilbreth.[5] The essential feature of the Taylor system was to analyse a process into its simplest elements and to time each element by stop-watch. The method of the quicker man was carefully studied and a resynthesis made incorporating the quickest elements into a new method. The emphasis by Gilbreth was more on the best way of carrying through a process by discarding what were thought to be unnecessary movements, the techniques employed being those of the cine-camera and the chronocyclegraph. Current techniques of time and motion study are based very largely on the methods developed by Taylor and Gilbreth. Out of the analysis made by time and motion study engineers have developed a number of so-called "principles of motion economy," and these principles seem to be based upon an underlying notion of saving time and effort.

When all the analysis, resynthesis, and trial and error processes have been completed, it is then necessary to make an allowance—the fatigue allowance—to cover rest, supervision, and personal needs. The allowance is usually in the form of a percentage of the total time standardised for the job, and its negotiation is a matter of bargaining which only too frequently goes outside the realms of physiology and experimental psychology.

Matthew thought that it should be possible to employ physiological criteria in order to build up standard times for various tasks, but he was sceptical as to the reliability or the repeatability of the physiological measurements with which he was familiar. He suggested that the metabolic cost of the work might be a useful guide to the rating of the difficulty of work and thought that the optimum rate of working as shown by the oxygen uptake might be an acceptable standard rate of working.

In comment on this suggestion, it should be pointed out that in a demonstration to the Physiological Society (December, 1950) Crowden, Das, Floyd, and Silver showed that the metabolic cost is not necessarily the best guide where a decision has to be made between alternative methods of performing work. They discussed two methods of weight-lifting, one of which was more economical in energy consumption. Electromyographic study of the two methods employed showed, however, that the choice really lay between a method having lower energy cost but imposing greater strain on the intervertebral ligaments, with consequent risk of injury to the discs, and a method of higher energy cost but with smaller risk of ligamentous injury. This principle has wide implications. Work of low metabolic cost which appears to be economical may be performed in such a way as to throw a heavy load upon a small group of muscles or other structure, which might therefore tire rapidly. An alternative method of performing the task although consuming more oxygen might distribute the load more widely over several muscle-groups and so diminish rather than increase fatigue.

Conditioned-reflex experiments, neurophysiological studies, and the laboratory experiments of the psychologist have all emphasised the unitary nature of movements and patterns of behaviour. This is particularly true of learned skills which comprise the great majority of work tasks in industry. There is an interrelation between the various elements of a skilled movement, and it is not possible to interchange or modify the elements in an arbitrary fashion, as would appear to be done by the time and motion study engineer, without risk of interference with the pattern of behaviour in a way which may be ultimately detrimental to the final objective. The sequences of movement represent the interplay of sensory information with motor performance; at every instant of the movement there is interplay which enables the individual to achieve his objective in his own individual way.

When an elemental movement is taken from one context and placed in another it does not follow that it still occupies the same time for completion. It has to be built into the new pattern, and this may result in considerable modification in both the movement itself and its temporal pattern.

Production and performance are well known to depend in large measure upon adequate illumination; but the practice of the production engineer, inevitably perhaps, lags behind the laboratory study of this problem. There is, however, a wider aspect of visual problems, summed up in the word "display," to which relatively little attention has been paid in time and motion studies or by the production engineer. The operative in many factory processes is confronted by a continuously changing set of information of a visual character, and his reactions have to be adapted to the situation of the moment. There is often scope for judgment, but relatively little attention would appear to have been paid to the visual factors affecting judgment and action except by the experimental psychologist. Study of the "display" problem in the factory is likely to result in a more scientific approach to the production problem. Conrad[6] has recently summarised the work of the Medical Research Council's applied psychology research unit in relation to this problem.

MEASUREMENT OF FATIGUE

A. T. WELFORD developed some of the points discussed by Sir Frederic Bartlett and others. When a task can be carried out in several different ways compensation for impairment of one function can be effected by a change in the manner of performance which throws the burden upon other less affected functions. When this occurs the first signs of impairment may actually be an increase of over-all achievement. R. C. BROWNE, for example, in his paper pointed out that sleep deprivation may initially stimulate performance.

Welford went on to say that some of the excessive demand is on the receptor mechanisms; errors will arise due to the extraction of too little information from the display, and actions may become jerky. Similar results may occur if the load upon the receptor functions is increased by anxiety or by awareness of aches and pains.

A somewhat different point from those considered above concerns the effect of fatigue upon learning new tasks. The method a subject builds up to deal with a new task depends partly upon the efficiency of the mechanisms he has available at the time. Impairment due to fatigue may dictate a method which is not optimal but which, once it is established, may be transferred to subsequent occasions even though the original fatigue is no longer present. The implications of this possibility for training are obvious.

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[2] Kjellberg, S. R., Rudhe, U., Sjöstrand, T. *Acta phys. scand.* 1949, 19, 136, 146, 152.

[3] Astrand, O. Experimental Studies of Physical Working Capacity in Relation to Sex and Age. *Copenhagen*, 1952.

[4] Taylor, F. W. Scientific Management. Harvard Business Studies, 1914.

[5] Gilbreth, F. B. Primer of Scientific Management. New York, 1914.

[6] Conrad, R. The Study of Skill by Motion and Time Study and by Psychological Experiment. 1951.

THERMAL FACTORS

T. **Bedford** discussed the effect of thermal environment, describing the earlier work carried out by Vernon and himself which showed how output and accidents were related to the temperature in the factory. As temperature rose or fell above or below the comfort zone both output and accidents increased. It needs to be stressed that although there will be dramatic declines in performance only at the extremes of temperature, yet significant changes occur when the temperature is only slightly raised or lowered.

G. P. **Crowden** described the pronounced changes of temperature and humidity which can occur in a domestic environment, and he showed that the housewife engaged in the family wash may soon be in a tropical atmosphere: considerable deterioration in performance results. This investigation indicated the importance of studying work in the house as well as the factory.

WORK CAPACITY OF THE STARVING

Ancel **Keys**, who was the director of the famous Minnesota experiment on the effects of starvation, discussed fatigue and work capacity in starving man.[7] His volunteers lived first on an adequate calorie intake of 3500 calories, on which they performed muscular work so that they kept in balance. They were then transferred to a diet of 1500 calories for a period of up to 9 months, and attempted to perform the same amount of work. Work capacity declined on the low-calorie diet, and Keys suggested from his studies that the decline was directly proportional to the decrease in the active muscle mass. He thought that the contractile muscle power was constant for a constant mass.

However, it should be pointed out that there are significant cardiovascular changes in starvation, as described by Howarth [8]; and indeed these were also found in the Minnesota study. Such changes may prove to be one of the limiting factors in starvation, as well as the change in the mass of active muscle.

VISUAL FATIGUE

H. C. **Weston** dealt with the importance of lighting in relation to "visual effort." He showed that when attention has to be concentrated in one part of the visual field, and the eye is subjected to a high level of brightness from another part of the field, the effort of attention leads to wrinkling of the face. The same subjects under the same illumination were found, however, to have a relaxed facial musculature when they were not required to pay attention. As a result of his wide experience of industrial situations where visual fatigue was said to arise, he had come to the conclusion that its avoidance was largely a question of the selection of operators so that the tasks which they have to perform fall within the range of their visual sensibility.

L. C. **Thomson**, in his review of the physiological aspects of visual fatigue, pointed out that there is no sharp division between the emmetropic eye and the defective eye. There are small defects of vision which are not corrected for, and the use of the term "normal" is quite arbitrary. There is, in fact, a continuous distribution ranging from hypermetropia through emmetropia to myopia. Some "normal" people have exceptionally good vision: but many, although able to perform well at ordinary fine tasks, fail at tasks requiring the highest precision, such as the alignment of pointers on a vernier scale—a task which can be performed accurately to a few seconds of arc. A similar situation exists in regard to visual activity which involves hue discrimination. That is to say, there are grades of colour blindness in a quantitative sense, and industrial tasks involving colour matching can only be carried out successfully by those whose colour-matching abilities, in the quantitative sense as well as the qualitative, fall within the required range.

Thomson emphasised that it is common to speak of weak eyes and straining the eyes, but in relation to the ear we say "hard of hearing" and accept the fact that the ear is just defective in hearing quality. He pointed out that it is not possible to strain or damage the eye in most of the uses to which the eye is put.

There are, of course, the notable exceptions of heat damage to the eye which may occur in certain industrial situations or as a result of looking at the sun. Cataracts may arise from exposure to radiations—e.g., neutrons and X rays. The problem of snow-blindness may also come in this category, but it is ill understood.

The difficulties of vision arise when the job calls for a higher grade of vision than the operative possesses. The way to avoid visual fatigue is to see that the operative has the sight necessary for the job.

ACTION-POTENTIALS

T. A. **Ryan** (Cornell) described experiments in his laboratory on the recording of muscle action-potentials from facial muscles and limb muscles in an attempt to find evidence of effort in visual tasks. With tasks of given difficulty no correlation was found with the level of illumination or with the distribution of illumination in the visual field, but with a fixed illumination there were changes in the action-potential discharges closely related to the internal difficulty of the task as judged by the psychologist. That muscle action-potential discharges are concomitants of effort may provide yet another method of assessing the "difficulty" of the task.

CONCLUSION

Although this symposium was inevitably discursive, it was a stimulating experience to attend it. The advances in many different fields, although not spectacular in themselves, when they are brought together certainly give hope that this intractable problem may be solved. There appears to be a strong belief that there are physiological changes in fatigue, if only they could be measured, and that these changes ought to be associated with the alterations in performance described by psychologists. Of the three criteria proposed by Sir Frederic Bartlett, the first at any rate—development of irregularity in muscle performance—should be susceptible to detailed physiological investigation.

Perhaps a general mistake is to regard fatigue as an evil. Sherrington [9] said in 1906:

> "Therefore . . . fatigue and freshness . . . are physiological factors influencing the result of the interaction of reflex arcs at a common path . . ."
>
> "Fatigue therefore in the long run advantageously redresses the balance of an otherwise unequal conflict. We can recognise in it another agency working toward that plastic alternation of activities which is characteristic of animal life and increases in it with ascent of the animal scale."
>
> "[Fatigue] seems a process elaborated and preserved in the selective evolution of the neural machinery."

O. G. **Edholm**
W. F. **Floyd**.

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[7] Keys, A., et al. The Biology of Human Starvation. Vol. I. Minneapolis, 1950.

[8] Howarth, S. Cardiac Output and the Peripheral Circulation. *Spec. Rep. Ser. med. Res. Coun., Lond.* no. 275, 1951; chap. 20.

[9] Sherrington, C. S. The Integrative Action of the Nervous System. London, 1947: pp. 224, 232.

In England Now

A Running Commentary by Peripatetic Correspondents

PEOPLE talk as if Leonardo's life was a succession of noble failures. They speak of machines and masterpieces that came to nothing and they mourn lost folios. It isn't reasonable. Leonardo created lavishly, like Nature, but at heart he was an experimenter and contemptuous of survival. The mark of the genius manqué is that he is so far in advance of his age as to be incomprehensible. By the time the public has caught up with his thought his idiom is out of date and has lost its appeal. Samuel Butler, the younger, is an example, and perhaps Whistler. But Leonardo is different. He is acceptable to every age. His creations sparkle through time like shooting stars, to light each era for a space and then vanish. The Renaissance had the benefit of his armouries and the *Last Supper*; we can enjoy the eddies of blood round the cardiac valves and the sublime countenance of St. Anne.

* * *

The final fellowship vivas at the Royal College of Surgeons are a rich source of material for the story-teller, whether his forte is Truth Nicely Told, like the asparagus tale from South Africa (March 29, p. 667), or Fiction Inspired by Fact. Here are two which, though unoriginal, are neither crude nor rude.

In the pathology viva the examiner looked up and saw that the next candidate was a nice-looking young man, rather shy, wearing the tie of the United Hospitals Sailing Club. His face seemed vaguely familiar, so as he sat down the examiner greeted him with "Good morning, Mr. Smith. I'm sure we have met before. Can you remember where it was?" "Yes, sir," replied the candidate, "it was at this table." This was an unfortunate start, and the examiner hastened to reassure him. "Never mind about that," he said lightly, "tell me the first question I asked you last time." "Yes, sir," said the young man, "you asked where you had seen my face before."

The second incident occurred during a viva in operative methods. The examiner asked the candidate how he would treat a fracture of the lower third of the humerus.

Cand. "I would put it in plaster, sir."

Exr. "How long would you leave it?"

Cand. "Six weeks, sir."

Exr. "What would you do then?"

Cand. "I should take off the plaster and X ray it."

Exr. "Suppose it hadn't united, what would you do?"

Cand. "I would put it into plaster, sir."

Exr. "For how long?"

Cand. "Six weeks, sir."

Exr. "What would you do then?"

Cand. "I would take off the plaster and X ray it."

Exr. And if it still was not united, what would you do next?"

Cand. "I should put it into plaster, sir."

Exr. "Look, Mr. Smith. How long are you going to spend putting this fracture into plaster and taking it out again?"

Cand. "I am going on till the bell rings, sir."

* * *

The Medical Art Society belong to that dwindling group of people who would rather have a dash at doing something themselves than talk about the way other people do it. Their annual exhibition of paintings and drawings, now in progress at Walker's Galleries, New Bond Street, is thus an adventure in character as well as in art. The picture of the year, to my mind, is a small grey affair, possibly a lithograph, by Brian O'Doherty, called "Waiting—On District, Rotunda," so unkindly hung that it has to be examined kneeling. It shows the simplified structure of a bored student, waiting for the simplified structure of a distant mother to wake up and get on with the pains; and it has pattern, character, and atmosphere. Still, I daresay it was a deal easier to do (given the eye to see the thing) than the competent water colours near it. Two nice sober examples are F. N. H. Maidment's "The mill road, Bosham," and Reginald Morshead's "Shoreham by Sea"; but there is less of an air of fluent habit about the grey-greens of Ian G. Robin's "Ilex avenue." "Lott's Cottage," as painted by Eric Topham, seems to have been done up since Constable had a go at it, and now has two dogs, one of them blue, in the garden; but it may be a different Lott. Stella Churchill paints for pleasure—and why not? Isabel Wilson saw a bleak little tree during her "Winter in London" and recorded it gracefully. Holmes Sellors fortunately knows more anatomy than appears from his "Street Scene," but the grouping is pleasant and odd, and the colours well placed; and Emanuel Miller's crayon of a man sleeping is very nice indeed.

The full-blooded will relish the cheerful vulgarity of R. H. Dale's "What do you mean—'forgot to put the film in the camera?'"—evidently a historic scene, only slightly caricatured, in some authentic operating-theatre. The gallery of students, behind their pane of glass, will perhaps give even more pleasure than the contending giants in the arena. The drawing of this is very clever, and so is that of Anthony Reford's "The toilet," with three stout pink ladies attempting to share a saucer of a bath; but the two pictures have little in common besides their exuberance, for one belongs to the students' magazine and the other to the eighteenth century.

On the whole the oil paintings are gallant rather than successful. Harold Avery, having given a convincing account of Copenhagen, shakes one's credulity with his too-blue water. Harold Gillies takes us with more assurance into some wild romantic country in Glen Clova and Norway; and A. B. Hewlett into the strangely orderly world he inhabits whether in France or anywhere else. Anthony Reford has done the head of a girl, a young grubby untidy girl, which is worth a good long look; and among the other portraits B. E. Barsby Smith's "Miss Plunkett" challenges one earnestly, like a woman doctor taking a case-history. W. G. Scott-Brown has some agreeable alpine scenes, and R. A. Bearer a very gloomy view of Marylebone, that most light-hearted and winning of stations. On the other hand Norman Ashton has robbed cacti of their sting in a thoroughly cheerful composition. The "River Test at Totton," according to Reginald Morshead, is full of still light, and could be lived with happily for a lifetime.

* * *

Science moves so fast these days that the older generation of surgeons cannot all be expected to keep up with the most recent mysteries of laboratory diagnosis. Thus when the discussion on a round turned to the Salmonellæ, our chief asked a student how the various species were identified, and received the concise reply: "By slide agglutination with monospecific antisera, Sir." "Oh, I see," said the surgeon in a voice that sounded ever so slightly vague. As they moved on to the next bed one of the firm remarked to a colleague: "I don't think he was quite with you there, old man."

* * *

I believe I have chanced on one of those new viewpoints that suddenly change the whole face of medicine, as one imagines oneself doing when reading about Hunter, Pasteur, and er—well, the other men who have made medical history.

I was gazing at my newborn infant at a time when I had been rereading my midwifery with the Canadian qualifying examinations in the offing. She looked confused and unhappy, as most infants do. Then in a flash it occurred to me why this was so. For at least two months she had lain head downwards in utero and now suddenly she had been forced into a horizontal attitude, or when not horizontal was held head upwards. Surely this sudden change must account for her confusion? Had she not suffered enough insults in parturition without this additional vasomotor disturbance?

Can I persuade the next generation to nurse and feed their babies upside down? I can foresee the hitherto resistant neonatal mortality figures at last tumbling down like the other mortality figures. My name may even be added in a footnote to the standard textbooks—who knows?

Letters to the Editor

APPOINTMENT AND QUALIFICATIONS OF CORONERS

SIR,—By the Coroners (Amendment) Act of 1926 no person may be appointed a coroner unless he is a barrister, solicitor, or legally qualified medical practitioner of not less than five years' standing in his profession.

This society, all the members of which are members of both the legal and the medical professions, is seriously disturbed at the fact that some local authorities, in whom the power of appointment is vested, are seeking to avoid or to limit the candidature of medical men for the appointment of coroner. In Essex, where a vacancy has recently occurred on the death of a distinguished and doubly qualified coroner, the county council has taken the retrograde step of inviting applications from barristers and solicitors only. In London, by a resolution of the County Council in 1937, future appointment of coroners was limited to those possessing legal qualifications of five years' standing or those possessing legal qualifications of less than five years together with medical qualifications of five years or more; and this resolution has been recently reinforced by a letter from the council to the London coroners stating that the same provisions will now be applied to the appointment of deputy coroners. My society feels that this decision will merely increase the very great difficulty which already exists in finding persons with appropriate qualifications who are willing and able to act as deputy coroners.

The greater part of a coroner's work is not done in open court, but in his office; in the populous districts in the jurisdiction of members of this society, more than three-quarters of the reported deaths are dealt with as non-inquest cases, after a post-mortem examination. In the reading and assessment of a pathological or a necropsy report it seems unlikely that any great advantage will be found in legal qualifications and experience, rather than those of the trained medical mind: and it is of interest that the ratio of inquest cases to non-inquest cases tends to be higher where the coroner has no medical knowledge or qualification.

I believe that a committee of the B.M.A. which considered, among other things, this very question was of the opinion that it was desirable that coroners should have both qualifications, but that they should certainly be medically qualified; the matter is clearly of importance to your readers, and to the public.

Westminster Coroner's Court,
Horseferry Road,
London, S.W.1.

C. J. F. BARON
Hon. Secretary,
London and Home Counties
Coroners' Society.

TRAFURIL

SIR,—I was greatly interested in the significant communication on the action of 'Trafuril' in rheumatoid arthritis, by Dr. Nassim and Mr. Banner (April 5). I have used trafuril in various forms since 1949, and some preliminary results have been reported.[1] The variation in skin reaction described by Dr. Nassim and Mr. Banner was noticed.

My personal experiments included the intramuscular injection of trafuril. This is usually followed by flushing of the face and upper extremities with, in some cases, loosening of the finger-joints and increase of the grip. It was seen, however, that occasionally the usual flushing and burning sensation of the face and forehead failed to appear, or were very slight, and there was no increase in mobility of the fingers or in power as recorded by the pleximeter.

More accurate assessment of the effect of trafuril should be possible by intramuscular injection than by application of the cream. Personally I now reserve the cream for personal use by the patient, who is directed to apply it to the myalgic spots, which of course may be quite remote from the pain area. If surface application is desirable in the consulting-room, I find that the tincture applied with an ordinary $^1/_2$ in.-wide paint-brush is equally effective, and pleasanter for the patient.

Here again the erythematous effect may be entirely absent. Hitherto, perhaps naturally, I have regarded this lack of response as having some connection with the type of epidermis, but now it appears that the cause may be much deeper and have a more fundamental significance. I agree with Dr. Nassim and Mr. Banner that the vasodilation is not mediated by histamine, as trafuril is perfectly well tolerated in extreme cases of histamine sensitivity; nor, I understand, is the effect obviated by the anti-histamine drugs.

I also have pleasure in recording the generosity of Messrs. Ciba Ltd. in providing the drug.

London, W.1. H. WARREN CROWE.

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[1] *Rheumatism*, 1951, 7, 75.

WHAT SHOULD THE NURSE BE TAUGHT?

SIR,—In their letter of April 5 Dr. Cropper and Mr. Houghton say that employment in hospitals should be available for girls leaving school who wish to nurse. Our experience is that the majority of girls who enter hospital at the age of 15 lose interest before they can begin their vocational training at 18, in order to become State-registered at 21. The girl of 15 who is interested in nursing should be advised to continue her general education, or, if that is impossible for economic reasons, to find remunerative work to do to fill in the time, the opportunities for this outside the hospital world being manifold. The work that is often suggested for these young girls inside the hospitals is, in many cases, being done by clerks, receptionists, and ward orderlies. Are these people to be thrown out of employment in order that work may be found for schoolgirls? If in the meantime these girls lose their interest in nursing, they will be no loss to the profession; for it is only those who have a real desire to help sick people that we want in our hospitals.

Your correspondents' second point is that the nursing curriculum should be limited to matters truly relevant to a nurse's duties. If this suggestion were adopted and theory was not taught, our nurses would be reduced to mere auxiliaries; but they would also be expected to carry out complicated treatments without any understanding of what they were doing. The danger of serious mistakes due to that lack of understanding would be bad enough, but even worse would be the effect on recruitment. Few intelligent girls of 18 who had passed their General Certificate of Education in a number of subjects at the ordinary or advanced level would consider entering a profession in which they were denied sufficient elementary knowledge to enable them to understand the more technical aspects of their calling. This state of affairs would arise at a time when opportunities for education beyond the normal school-leaving age are open to an increasing number of girls. Many hospitals in this country have the opportunity of recruiting an average of 100 girls of this educational standard each year.

Most of these girls, if they followed the curricula laid down by some of the Canadian and American Schools of Nursing, could quite easily obtain a degree in nursing. But the student nurses in this country prefer to nurse the patients. The suggestion that our system of training is too theoretical is a great exaggeration. In her first year the student nurse spends her time ministering to the fundamental needs of her patients—blanket-bathing, bedmaking, bedpan rounds, &c. Meanwhile, as she gains more confidence, she watches and is given instruction in more responsible treatments—giving injections, doing dressings, &c.—which she does by herself in her second year. In her third year she develops her skill and is given some responsibility for the simple work of her juniors. The result is a competent, intelligent nurse in whose care physicians and surgeons can leave their patients with confidence.

I cannot understand why Dr. Cropper and Mr. Houghton think that the Preliminary Training School period is a cause of wastage. I have spoken to hundreds of nurses about this, and without exception they thoroughly enjoy that part of their training.

As to the psychological aspect of nursing, student nurses do in fact have a few lectures in elementary psychology; but the real understanding of the patients' mental needs can only be learnt by the example of the trained nurses and the doctors, and it is unfortunate that sometimes, under the stress of events, both of these fail in this respect.

Your leading article showed, in my view, more understanding of the knowledge and training required by the nurse if she is to be a real help to the doctor on both the human and scientific sides of his work.

London. M. MARRIOTT.

SIR,—The Matron of Addenbrooke's calls attention to an old evil in modern dress when she speaks of "far too many hospitals where, for lack of other staff, young girls are employed in actual nursing duties not only on day but on night duty." Over the past twenty years you have allowed me space to record instances that had come to my notice, as one child after another in mid-teens had been sucked into hospital or nursing-home service to emerge stricken for death, or long invalidity, by some form of tuberculosis. Such cases seemed to be "just one of those things" of which contemporaries take little note but which historians paint in flaming colours.

Miss Ottley dares to take the historic view when she states "in our twentieth-century health service children are engaged in nursing the sick. Can we, of all people, members of the medical and nursing professions view such a situation with equanimity?"

Moor Park, Herts. ESTHER CARLING.

SIR,—The Cropper-Houghton syndrome (April 5, p. 716) is only one manifestation of a more widely spread malady—morbus academicus, or foie-gras disease. Its root cause is the vested interest of the academies, a very powerful interest, and no less powerful for being largely unconscious. Most teachers agree cordially that the curriculum is overloaded; few will *do* anything about it. The dead leaves are all in the other man's quadrangle, and any suggestion that a broom could be used in their own little nooks will be fiercely opposed.

There are many dead leaves, indeed whole dead branches; a broom is not enough; saw, shears, and pruning-hook are needed as well. There is failure to discriminate between principles, which must be learned, and the details which illustrate them; between facts important to nurses, and facts important to physiologists, bacteriologists, biochemists, surgeons, physicians, gynæcologists, and all the other people who help the nurse to care for the sick; and between facts immediately necessary for doing her daily work, and facts she can look up if she has to, about which it is enough to know where they can be found.

But let nurses be glad of two things: they are young enough to forget, and at least they are not medical students—the most incomparably stuffed geese of our generation.

Giggleswick, Settle,
Yorkshire. D. P. LAMBERT.

CEREBRAL SYMPTOMS IN CARDIAC INFARCTION

SIR,—The case described by Dr. Batty Shaw (April 12) suggests that the symptoms of left cerebral dysfunction followed an anoxic tissue acidity (due to the sudden fall of blood-pressure), engendered by the vascular reactions to the right-sided old softening.

Similar brain dysfunction with mental or neurological symptoms also follows other cardiovascular derangements, as in our mental patients. They are analogous to the cases of mesencephalitis described by Dr. Bickerstaff and Professor Cloake.[1] These associated clinical and necropsy (or deduced) findings are understandable from the viewpoint of my book.[2]

Birmingham. F. A. PICKWORTH.

BENIGN LYMPHOCYTIC MENINGITIS IN CO. DURHAM

SIR,—In the article by Dr. Smith and Dr. Kinsella[3] I was surprised to read: "Benign lymphocytic meningitis was provisionally diagnosed, but owing to the anxiety of the parents and the obvious illness of the child it was felt justifiable to make a lumbar puncture."

The differential diagnosis of benign lymphocytic meningitis is tuberculous meningitis, and these two conditions can be differentiated only by lumbar puncture. With streptomycin available for the treatment of tuberculous meningitis, not to exclude this diagnosis as early as possible would be folly.

Central Islip State Hospital,
New York, U.S.A. M. G. JACOBY.

LEONARDO'S LEFT HAND

SIR,—I have read with interest Mr. Capener's *article* last week. Why were all the legends in Leonardo's drawings written, not in ordinary Italian script, but in "mirror-writing" with the words read, and spelt, and each letter pointing, from right to left? This question was posed also at the Osler Club Symposium on Leonardo da Vinci but brought forth an equivocal reply.

It could not be a mere cryptogram, though it would make the script difficult to decipher and tedious to read—certainly to any onlooker!

I venture to suggest the following explanation for the use of the "mirror-writing." Leonardo received no regular education in his youth (in which and many other respects a parallel can be drawn between his life and that of our own celebrated John Hunter). He knew no Greek. His contemporary biographer comments on his lack of knowledge of Latin. The only other language known to his erudite contemporaries was Hebrew (even in the *Fabrica* of Vesalius, in 1543 and 1555 editions, Hebrew words adorn some of the full plates). The words of this language are spelt, read, and written, while the letters tend to point, from right to left, the paging being in the same direction. There is no reason to think that Leonardo was unfamiliar with these facts, while his left-handedness would render it more natural to adopt these hebraic literary characteristics.

Another point would have influenced him. All books had to be published in Latin. Certainly the *vernacular* was taboo. He could not use Italian. It will be remembered that a storm of criticism broke about the head of the famous French physician Jean Fernel in the fifteenth century, when he created a precedent by publishing one of his later medical works in the vernacular French. One of the reasons adduced in favour of retaining Latin as the language of medical publications was to prevent this knowledge reaching the illiterate barber surgeons, who were unversed in the Latin tongue. When Fernel was charged with thus bringing medical knowledge to the surgeon, his retort was: "Fear not, for the barber surgeons cannot even read French."

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[1] Bickerstaff, E. R., Cloake, P. C. P. *Brit. med. J.* 1951, ii, 77, 362.

[2] New Outlook on Mental Diseases. Bristol, 1951.

[3] Smith, R. C. F., Kinsella, J. J. *Lancet*, 1951, ii, 882.

The type of cryptogram first introduced by Leonardo has a subsequent parallel. In the archives of the Cavendish Laboratories at Cambridge, there are preserved some letters by the famous mathematician Clerk Maxwell, in which he writes many of his English words using the Greek hieroglyphics—a manœuvre I have on occasion used in the past in my hospital outpatient case-records to preserve my unpalatable diagnoses from the prying eye of the νευρασθενικ patient.

London, W.1. N. ASHERSON.

A.C.T.H. IN ERYTHEMA MULTIFORME EXUDATIVUM MAJOR

(STEVENS-JOHNSON SYNDROME)

SIR,—The ætiology of erythema multiforme exudativum remains obscure and treatment largely unsatisfactory. Recent publications have dealt with the history, nomenclature, and ætiology of the condition.[1,2] The name "Stevens-Johnson syndrome" has been suggested for the major or severe form, and the suffix "Hebra" for the mild form without stomatitis and ophthalmia.

Efforts to find a virus or other infectious agent have been inconclusive or negative. A virus has been sought without success in the usual laboratory animals and in horses, cows, sheep, pigs, and embryonated eggs.[3,4]

In 1950 we saw an 8-month-old boy with characteristic erythema multiforme exudativum major, with polymorphous rash, oral ulceration, conjunctivitis, keratitis, balanitis, and extensive pneumonitis. He had become progressively worse during 2 months' treatment with antibiotics, sulphonamides, blood-transfusions, and dietary alterations. On the premise that sensitisation may play an important part in the evolution of this syndrome, he was given adrenocorticotropic hormone (A.C.T.H.) (Armour). There was a striking response within 4 days, and the lesions began to clear up.

The illness began on Aug. 30, 1950, with cough and rhinitis, succeeded in a few days by vesicular lesions in the mouth and on the scrotum, followed shortly by conjunctivitis, keratitis, irregular fever, rapid loss of weight, and radiographic signs of scattered density in both lungs. Before having A.C.T.H. he received sulphadiazine, penicillin, streptomycin, aureomycin, chloramphenicol, repeated blood-transfusions, and soya-bean and casein digest substitutes instead of a cow's milk diet. Fever was irregular, weight loss progressive, and pulmonary signs, both clinical and radiographic, continued for 2 months. Local therapy (antibiotics, gentian-violet, drying lotions) did not modify the course of the illness.

Bacteriological examination of the blood, saliva, urine, and ocular exudate was negative. The bone-marrow was normal; red-cell counts showed a mild hypochromic anæmia; white-cell counts ranged from 10,500 to 27,200 in ten counts, and no eosinophils were seen except on Sept. 19 when they numbered 5% of a total of 14,000 cells.

On Oct. 25 he was given 20 mg. of A.C.T.H. every 6 hours. Within 4 days the oral and ocular lesions began to resolve. A radiograph of the chest taken after 5 days' treatment with A.C.T.H. showed a remarkable change. A film taken just before treatment showed "involvement of all lobes, the uppers most severely; consistent with a clinical diagnosis of fungus infection." The next film showed "marked improvement and resolution in all involved areas." The dosage of A.C.T.H. was reduced to 15 mg. every 6 hours on Oct. 30 and to 10 mg. every 8 hours on Nov. 6. It was stopped altogether on Nov. 13. A follow-up note and photograph one year later indicated normal growth and development with no recurrence of symptoms or signs.

A considerable effort has been made to find an infectious agent responsible for this syndrome. Maculopapular forms of erythema multiforme have been observed in a variety of infectious diseases, but none simulating the complete picture of erythema multiforme exudativum major. Such rashes are generally ascribed to an allergic response to the infecting organism. One of us has seen a child who, during the course of acute primary herpetic gingivostomatitis in which the herpes virus was isolated and there was a rise in the specific antibody titre, developed erythema multiforme of the more usual type, as seen occasionally during the course of various infections. The picture could scarcely be confused with erythema multiforme exudativum major, despite the gingivostomatitis.

We think that the ætiology of this condition is multiple, but that sensitisation is important. Under such circumstances A.C.T.H. or cortisone should be effective. In the presence of mucosal lesions of this type antibiotics orally may be ineffective and even risky.[5]

University of Louisville,
Kentucky.

ALEX J. STEIGMAN
J. J. KELLY.

TREATMENT OF SCARLET FEVER

SIR,—It appears that in 1950 there were 65,883 cases of scarlet fever notified in England and Wales, compared with 56,851 cases in the whole of the United States. A World Health Organisation survey[6] concludes that "Europe is still the world epidemic centre" for scarlet fever; but I believe that these figures may more truly represent the enlightenment on the other side of the Atlantic in making no diagnostic distinction between streptococcal throat infections accompanied by a rash and those not so accompanied.

Hildenborough, Kent. C. GLAISHER.

AN UNUSUAL EPIDEMIC

SIR,—I have been extremely interested by the many letters reporting cases of an "unusual epidemic." This illness is apparently not limited to England; and in the past two months I have seen about 35 such cases, which I am tempted to call encephalitis.

The clinical picture is variable, but the most prevalent symptoms are headache and vertigo. The headache is not very acute, and in many cases it is more a vague feeling of heaviness. Often the patients complain of pain at the back of the head and in the neck, and pressure on the point of emergence of the great occipital nerve is generally painful. Vertigo is commonly also present, though it may be lacking; in my experience it is generally mild, however long it may last.

A few patients have complained of temporary impairment of their mental faculties. A woman told me that, having to add up a few figures, she said: "five and five make thirteen"; and a man was worried because he could not write an ordinary letter without making a mistake every other line. In no case was the headache strong enough to explain per se these other troubles. Occasionally I have noticed stiffness of the neck and—especially in children—positive Kernig's sign.

In one case only were the symptoms severe enough to warrant a lumbar puncture, and the cerebrospinal fluid was almost normal.

Curiously enough, for a disease which seems to be contagious, I have never met two cases of it in the same household. This may be explained by the existence of subclinical forms, as I heard of people having suffered from headache for a day or two only.

Intravenous injections of sodium salicylate may not be entirely devoid of effect; but aureomycin seems specially useful. A large number of patients quickly recovered after 2 g. a day for 4–5 days, whilst untreated cases may apparently last 2–3 months.

The impression is that this is a viral disease. Whether all the cases reported in your columns are of the same disease, and whether the epidemic I have seen in

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[1] Ashby, D. W., Lazar, T. *Lancet*, 1951, i, 1091.

[2] *J. Amer. med. Ass.* 1951, 146, 1424.

[3] Commission on Acute Respiratory Diseases. *Arch. intern. Med.* 1946, 78, 687.

[4] Anderson, J. A., Bolin, V. *Arch. Derm. Syph., Chicago*, 1949, 59, 251

[5] *Lancet*, 1951, ii, 532.

[6] See *Times*, April 19, 1952.

Normandy is related to the "unusual epidemic" you describe, is more than I can tell. But all our patients have a few features in common.

Messel, Orne, France. GABRIEL MOUCHOT.

AGE AT ONSET OF TUBERCULOSIS

SIR,—Your leading article on contact examination (March 8) points out the difficulty, and importance, of fixing the age at which the risk of tuberculosis increases. It is agreed that resistance to the disease is lowered during the period of sexual development, and that ideally the incidence should be related to physiological rather than chronological age. The term "puberty" (which means the state of being capable of procreation; legally, in this country, achieved at the age of 14 years in boys and 12 years in girls) is commonly used rather vaguely to describe the period of transition from childhood to adolescence. Some degree of accuracy may be obtained in females by using the *menarche* as a fixed point, but no such convenient incident occurs in males. In practice, therefore, the use of puberty as an epidemiological landmark must be considered unsatisfactory. Furthermore, as your article emphasises, the Ministry of Health age-group classifications are not ideal, though they probably are the best that can be contrived for the analysis of large-scale notification figures.

A more rewarding line of approach is to study the clinical histories of children with manifest phthisis (progressive pulmonary tuberculosis of "adult" type).

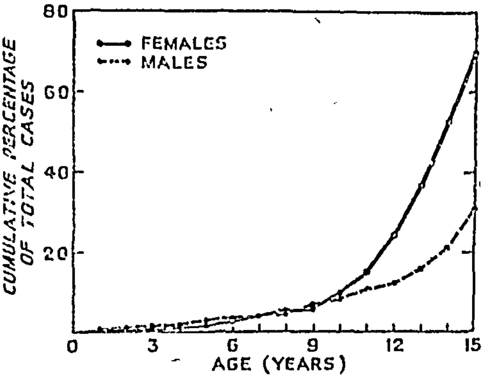

Fig. 1—Average age on diagnosis of pulmonary tuberculosis in five series in the U.S.A. and Germany (a total of 614 cases).

Since the discovery of such disease nearly always leads to early treatment, sanatorium and clinic records should yield the age of each individual at the time of diagnosis. Reports of such investigations have been published in America by Chadwick and Zacks,[1] Gibson and Carroll,[2] Karan,[3] and Morgan,[4] and in Germany by Piotsch.[5] The averages from these five reports are shown in fig. 1. The graph from each approximates closely to the average. Fig. 2 illustrates the findings in a series of 60 personally collected cases from Poole Sanatorium and the neighbouring chest clinics, observed during the period 1938–51. In all the reports the patients were white children.

Several points of interest emerge from all these series:

1. Only about 13% of the cases of phthisis in children occur below 10 years of age, and the sex-incidence in these is equal.

2. In girls the incidence rises sharply after the age of 10 years.

3. A less distinct rise in boys is seen after the age of 12 years, and the male graph roughly parallels the female with an interval of 2 years.

4. Between 11 years and 15 years there are nearly three times as many cases in females as in males.

If this analysis is acceptable, one may say with some confidence that the age at which the risk of tuberculosis begins to increase is 10 years in girls, and, less definitely, 12 years in boys. The striking agreement in age-incidence between the six reports, despite differences of race and environment (racial differences in the age at puberty are probably not great), seems to give authority to this observation.

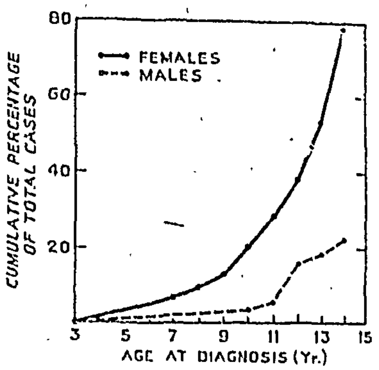

Fig. 2—Age on diagnosis of pulmonary tuberculosis in 60 cases in North-East England.

The low total incidence of phthisis in childhood reported in the two publications referred to in your leading article can be confirmed from other sources. Combined information from notifications, tuberculin surveys, mass radiography, and published work on this subject suggest a total incidence in tuberculin-positive white children of not more than 0·1% below 10 years of age, rising at 15 years to about 0·5% in girls, and 0·2% in boys.

Poole Sanatorium,
Nunthorpe, near Middlesbrough. J. P. ANDERSON.

RHESUS NOMENCLATURE

SIR,—Since my letter appeared on Feb. 2, I have encountered numerous other C-D-E equivalents for the phenotype Rh_1rh, in addition to the dozen previously listed. Some of these are

$$\frac{CDo}{o\quad o},\ CDoco,\ \overset{+}{C}\overset{+}{D}\overset{-}{E}\overset{+}{o}\overset{+}{d}\overset{+}{o}.$$

It is *significant that only a single champion* has come forward to defend the Fisher-Race notations. As his "solution," Dr. Allan (March 22) suggests still another modification of the C-D-E notations, thus confounding confusion.

Brooklyn, New York, U.S.A. A. S. WIENER.

MORE MANURE

SIR,—Yours are not the columns in which to compare the merits of "muck and magic" with the views of the devotees of hydroponics, but we are all sensitive to the prospects of our food-supply. The county engineer of Dumfries, to whom you refer in your annotation of April 12, is to be congratulated on a practical attempt to remedy one effect of the agricultural tractor; and, whilst doctors are understandably more concerned with the pathogenic bacteria, there is a view that the compost heap and farmyard manure owe their usefulness to the contribution that is made to the bacterial flora of the soil, for there is no reason to assume that the *soil flora* is always self-balancing.

It would be a pity if the innocence of the Dumfries compost failed to be proved and the matter were abandoned; for, whilst the presence of pathogens is demonstrable in our sewage effluents, this may be a reflection more of existing treatment difficulties. If these matters needed exploration one would suggest that the sewage from a sanatorium or general hospital might provide an abundance of testing material, but against this bacteriologists would be saddened by the thought of the mass of antiseptic which goes down the same drains. It sometimes happens that a new hospital or sanatorium is

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1. Chadwick, H. D., Zacks, D. *J. Amer. med. Ass.* 1927, 89, 670.
2. Gibson, C. B., Carroll, W. E. *Amer. Rev. Tuberc.* 1927, 15, 665.
3. Karan, A. A. *Ibid*, 1932, 26, 571.
4. Morgan, R. *Ibid*, 1934, 29, 577.
5. Piotsch, W. *Z. Tuberk.* 1939, 82, 28.

built in a position which requires its own sewage treatment plant. In such a new building drains or part of them might be kept separate so that, whilst in ordinary circumstances they would be combined to pass through an orthodox purifying system, it would be practicable to divert some effluents to other treatment plant in which the full effects of anaerobic and aerobic treatment could be explored and the means for their effectiveness against pathogenic bacteria established.

London, S.E.1. J. H. OLIVER.

VARICOSE ULCERS

SIR,—As a "bad leg" doctor, I rejoice in the use of the term in your annotation of April 5. There is, however, little else of note to fire the enthusiasm of the surgeon or kindle the spark of epithelium upon the patient. This is a great pity, for your annotations rank with the special articles in the *Times*, exerting within their sphere a profound influence, as does gravity, upon informed medical opinion the world over.

It is thus doubly sad to see the patent misconceptions of a bygone era disinterred from the slag-heap of medical progress and revivified as modern ghouls. One of these dismal spectres declares that varicose ulcers can only be healed if the patient remains in bed, either at home or in hospital. This statement so belittles the achievements of both this and the last century, that it is hard to believe it is not a misprint. Surely by now we have all heard of ambulatory elastic adhesive compression, whereby the patient can continue full-time work whilst his ulcer heals. I have yet to see a *varicose* ulcer (and I have now seen enough to satisfy even the statisticians) which will not heal under this treatment, the patient pursuing his own occupation with maximal vigour—and yet we are told to put them to bed. What a waste of time and money, and what a waste of a bed! And what of our geriatric patients with varicose ulcers? Are we to keep them in bed and watch their ulcers healing whilst their joints stiffen? Fortunately this, too, is unnecessary, for with slight modifications, as befits the dignity of old age, the same technique will deal with the ulcer on an ambulatory outpatient basis.

I was disappointed, but not surprised, to see no references to any evidence in favour of the endocrine theory of causation of varicose veins so prominently featured in your annotation. This old surgeon's tale, handed on from consultant to houseman, has yet to be substantiated by concrete fact. I am at the moment engaged in an investigation into varicose veins in pregnancy which has proved to have some most interesting facets, not the least being that varicose veins *appearing for the first time* rarely declare themselves until the uterus is large enough to play a mechanical part in the production of venous engorgement of the lower limbs. As for the hitherto uncharted range of varicose peaks that you have opened up before us, such maps as I have in my possession, whilst showing the Everest of pregnancy give no indication of the Pyrénées of puberty nor the Matterhorn of the menopause; for although we see patients whose veins appear at these times, far from being a peak they are a valley.

I trust, Sir, that it was compositor's cunning, rather than editorial intention, that gave injection precedence over surgery in your list of efficient treatments; for despite the fascinating craze of the late '20s and early '30s follow-up studies have convinced most ardent sclerosers that injection, as a primary measure, is followed by a recurrence-rate of over 80%. Surgical measures, you may retort, are equally useless; and if you are referring to the usual surgical measures in the average hospital, I am with you heart and soul. For what happens to patients who present themselves for treatment? They state they have "veins"; they are asked to raise the trouser leg, or lift the skirt, just to ensure that their diagnosis is correct, and then they are placed on the waiting-list. When they are admitted, the standard blunderbuss procedure holding favour at the time of operation is carried out irrespective of the type of veins present; and not unnaturally the veins recur.

The most important, and the most neglected, aspect of the treatment of varicose veins is to examine the patient, classify the veins, and institute treatment appropriate to the type. I have tried[1] to set down clearly the simple basic principles upon which the examination is based, and I am delighted to say that this cry in the wilderness has been well received. You end by saying that the subject of varices is one on which some medical education of the public would be useful and constructive; I should prefer to see those who will carry out the treatment instructed first.

London, W.1. STANLEY RIVLIN.

SIR,—Your annotation suggests that patients with varicose ulcers do not take them seriously, but accept them fatalistically. I am convinced that these unfortunate people do take their ulcers seriously and are only fatalistic because they receive so little help from the medical profession.

The reasons for our impotence in the treatment of leg ulcers seem to lie in the failure to understand their fundamental cause. This point is illustrated by your annotation, which might well have been written between 1800 and 1867 when surgeons became obsessed with the importance of superficial varicose veins and John Gay's important monograph[2] had not been published.

Leg ulcers result from defective circulation in the lower limb. It has long been appreciated that the weight of the column of blood in the arteries counterbalances that in the veins, in whatever position the body may be. But in spite of this balance, and although there is a *vis a tergo* represented by the capillary pressure when the patient is lying prone, relay-pumping is required in the erect posture to maintain a satisfactory return of blood from the lower part of the legs. Harvey described how the movement of the limbs and contraction of their muscles squeezes the blood through the veins towards the heart. When the calf-muscles contract the venous blood is forced upwards into the iliofemoral veins and cannot flow back, when the muscles relax, on account of the valves in the veins, as Richard Wiseman appreciated in 1676.[3] Thus there is an efficient pump—the leg-muscle pump—helping to return blood from the lower limb during exercise.

The cause of leg ulcers is failure of the leg-muscle pump, though occasionally, as Gay realised, arterial disease may play a part. The leg-muscle pump may fail owing to blockage of the deep veins by thrombosis; by incompetence of the valves of the deep veins by dilatation; or by destruction of the valves from thrombosis and recanalisation. Lack of muscular contraction with prolonged standing in one position or with arthritis of the knees or ankles may also result in failure of this pump. Such failure causes increased capillary pressure in the leg with œdema, induration, and ulceration. Superficial varicose veins, unaccompanied by dilatation of the deep veins, do not cause failure of the leg-muscle pump and are never responsible for ulceration.

In a series of 750 patients with leg ulcers, examined personally, the cause of failure of the leg-muscle pump was venous thrombosis in 79%, and varicosity of deep veins in 7·6%; and in 10·4% the cause was doubtful. Arterial disease or arthritis accounted for the remainder.

In the prevention of leg ulcers the prevention of venous thrombosis is of paramount importance. Prevention of

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1. Rivlin, S. The Treatment of Varicose Veins and their Complications. London, 1951.
2. Gay, J. On Varicose Diseases of the Lower Extremities. The Lettsomian Lectures of 1867. London, 1868.
3. Wiseman, R. Severall Chirurgicall Treatises. London, 1676.

ulcers does not depend, as your annotation states, on early and efficient treatment of varicose veins. When the leg-muscle pump has failed, from whatever cause, ulceration can be prevented if the œdema is controlled by elastic support.

Once ulceration has appeared, early treatment is important. The longer an ulcer remains untreated the more difficult is its cure. With the exception of ulcers of many years' duration, with much induration of the leg, which may require rest in bed, it is only necessary to abolish the œdema and the ulcer will heal.

Rest in bed has serious social and economic disadvantages for most patients and carries a risk of venous thrombosis and stiffening of the ankle-joint. The value of surgery in the treatment is still uncertain. Until a defective leg-muscle pump can be repaired control of œdema by compression and massage by Bisgaard's method offers the best chance of cure. Unless aftercare is adequate relapse is probable and permanent support by bandages or elastic stockings is required. As yet no surgical treatment can offer an alternative.

It is high time that we appreciated that treatment of superficial varicose veins is no answer to the problem of leg ulcers. Moreover, it is sometimes the cause of ulceration, as in 33 patients (4·4%) in my series in whom deep thrombosis followed injection of varicose veins, and in 10 patients in whom ulceration was precipitated by saphenous ligation. In another 49 patients ulceration became worse or appeared after such ligation.

Leeds. S. T. ANNING.

POSSIBLE DANGER WITH CYCLOPROPANE

SIR,—Safety First has long been the slogan of anæsthetists, and it is with this in mind that I would like to point out a danger from cyclopropane with the machines in use at most hospitals.

The rotameters of nitrous oxide, oxygen, and carbon dioxide are controlled by means of a screw-valve situated at their base, but in the case of cyclopropane this adjustment is affected by means of a circular key on top of the cylinder of cyclopropane on the side of the machine. A movement of as little as 1 cm. is sufficient to turn on the cyclopropane from 0 to 750 c.cm. per min.; and on many of the older cylinders this is achieved by the slightest touch.

A nurse or orderly brushing past the machine in the theatre, or during the transit from anæsthetic room to theatre, can quite easily turn this delicate control either off or full on. Especially dangerous is the fact that the gas is sometimes accidentally turned on when the anæsthetist has not intended its use, and when, therefore, his eyes will not be as often as usual on that rotameter, which is in any case much smaller than the others.

Conversations with anæsthetist colleagues have shown that these accidents are by no means rare, and in my opinion the provision of a guard round the cyclopropane key is not a sufficient safeguard. For absolute safety the cyclopropane rotameter should be provided with a separate screw-valve of its own.

West Hartlepool. FRANK R. RUSSELL.

CORONARY AND MYOCARDIAL DISEASE

SIR,—In your issue of April 12, Dr. W. P. D. Logan contrasts the mortality-rates in different social classes from "coronary" and "myocardial" diseases, and in the second paragraph he defines coronary disease as including angina pectoris, and myocardial disease as myocardial and cardiovascular degeneration. Unless I am mistaken these terms all refer to the same pathological entity—namely myocardial ischæmia due to coronary atherosclerosis.

The terms used are, of course, those of our colleagues who certified the cause of death. In the case of terms such as coronary atheroma, coronary thrombosis, or angina pectoris, the meaning is clear. In the case of myocardial or cardiovascular degeneration the exact meaning is rather vague; but I do not see that there is any other likely meaning than degeneration of the myocardium due to ischæmia produced by coronary disease. It might be argued that the two sets of terms refer to coronary thrombosis and to coronary atherosclerosis without thrombosis, but this is a distinction that is difficult if not impossible to make even at necropsy and certainly cannot be made clinically.

May I suggest that it would aid clearer thinking if we used the term "ischæmic heart-disease" for all cases where we mean that the heart has failed for lack of a proper blood-supply?

Department of Pathology,
Postgraduate Medical School of London,
W.12. C. V. HARRISON.

RADIOLOGICAL INVESTIGATION

SIR,—I was very pleased to see that Dr. Peter Leggat (April 19) had given such prominence to my statement: "The fact that young adults die from undiagnosed pulmonary tuberculosis is not due to failure to radiograph them, but to *bad clinical examination*." The statement is based on many years' experience with sound clinicians, and on such evidence as I have previously recorded of young soldiers. These men's chest complaints were dismissed by their medical officers (not old medical practitioners); but when they went home on leave their non-medical parents recognised the disease and took them to the family doctor, who supported the diagnosis and had it confirmed by radiography or sputum examination. No mass radiography of soldiers will prevent this: bad clinical work is usually associated with bad radiology.

I have repeatedly examined patients sent by general practitioners who rightly detected the early signs and symptoms of tuberculosis, though I could find no signs of it at the first examination, or only minimal signs. (And when I say minimal I mean less radiographic evidence than some "mass workers" record under that term; for they include not only old lesions but such as sometimes vanish within a few weeks without any treatment. I have seen that lobectomy has been performed on such within a few days of discovery. What a remarkable "advance" in the treatment of tuberculosis, and *what clinicians!*)

I am not at all surprised to note that in a recent survey on minimal pulmonary tuberculosis Dr. Leggat discovered that "in over 60% of the cases there were no symptoms and in over 70% there were no signs." I should have expected his figures to be nearer 100%. I have seen some patients, who because of their suspicious signs were referred by general practitioners to the chest expert, returned as normal; yet the parents were convinced that the disease was present, and I have established the diagnosis. When he does not observe the early radiographic signs, the "expert" sometimes becomes *blind* to the clinical evidence detected by the dctor, patient, and parents.

If Dr. Leggat examines the figures of the Birmingham mass-radiography unit recorded by Dr. Halliday Sutherland,[1] he will see that of the 157 cases of tuberculosis detected, 125 were found to have tubercle bacilli in the sputum. As regards the other 32 cases, *it remains to be proved* that the disease was active and that, undiscovered by radiography, they would not have healed without any treatment or knowledge of the disease, as the greater majority of lesions do. Further, these *examinations*, though conducted with a mass-radiography unit, did not constitute mass radiography but an essential part of a clinical examination which general practitioners sought for patients in whom they had found signs—a very proper, reasonable, and economical method which was suggested by a radiologist[2] who has strongly criticised mass radiography *from its inception*.

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[1] *Lancet*, Jan. 19, 1952, p. 152.
[2] Brailsford, J. F. *Med. World, Lond.* March 31, 1934.

With Dr. Leggat's concluding remark "but the ultimate responsibility in regard to treatment lies with the clinician" I fully agree. If that responsibility was forced home on all those who call themselves clinicians we should see fewer patients who had no signs and symptoms before radiography, but now, after treatment, have more signs and symptoms than is reasonable or justifiable.

Birmingham. JAMES F. BRAILSFORD.

THE DENTISTS BILL

SIR,—Mr. Roper-Hall's letter arguing against the proposal in the Dentists Bill to carry out an experiment in the training and employment of dental ancillaries, and criticising your leading article of March 29, was surprising; for its author was a member of the United Kingdom Mission which went out to New Zealand in 1950 to study the operation of the school dental service there. The New Zealand service has depended for the last thirty years upon the use of school dental nurses such as it is now proposed to employ for an experimental period in this country. The group of eminent dentists who comprised the mission were unanimous and cordial in their appreciation of the functioning of the service, of the value of the school dental nurse as an educator in oral health, and of the quality of her work. The proposals of the Dentists Bill are a consequence of their unanimously favourable report. One wonders why, at this late stage, Mr. Roper-Hall has come to the conclusion that the New Zealand experience is irrelevant to the grave crisis affecting the school dental service here. He can hardly entertain illusions as to the seriousness of this crisis, nor believe it to be less acute or in some way less permanent than that facing the health authorities in New Zealand thirty years ago.

The service has never at any time been able to recruit more than a fraction of the dentists it needed to provide adequate treatment—a state of affairs which remained largely unnoticed until, with the inception of the National Health Service, numbers of the already totally inadequate personnel were attracted away from the service to lucrative private practice. The over-all shortage of dentists and the understandable reluctance of all but a minority of them to undertake the exacting and repetitive tasks of routine children's dentistry will only be offset when ancillary workers are trained to perform the simpler of these routine tasks under the direct supervision of a qualified children's dentist, who would plan the treatment for each child, delegate to the dental nurse that part of the treatment she has been trained to perform, supervise her work, and do the more complicated operations himself. Teams of a dental officer and five or six dental nurses could in this way really begin to offer an acceptable service to the children under their care, making the most economical use of available skill. As a dentist who has already spent too many years in a discouraging struggle against dental decay in children, and conscious of having made no real impression on the problem of their dental health, I not only welcome the Dentists Bill but believe firmly that only by enlisting the help of ancillaries shall we ever be able to build up a children's dental service of which the country can be proud.

Mr. H. W. Breese (April 12) wonders why it should be necessary for a qualified dentist to supervise the work of the dental ancillaries, since the latter would be specialists in the limited field of children's dentistry. In fact, they would be specialists in the filling and extraction of children's teeth only, which I am sure your correspondent would agree is by no means the whole field of children's dentistry. Unfortunately, under present conditions, the school dentist has little time for anything but this limited routine work, so great is the pressure upon him. The children's dentist in charge of a team of ancillaries would supply the medical knowledge which had been deliberately excluded from the dental nurse's training. Relieved of much of the routine work, which an ancillary trained specifically for the purpose could perform equally well and at much less cost, the dental surgeon would be enabled to give the benefit of his wider knowledge to many more children than he can ever hope to reach at the present moment.

Any realistic discussion of the economic aspects of this problem cannot ignore this factor. It can hardly be overemphasised that the present system, in which school dentists after an expensive training of five years spent acquiring a background of medical knowledge and an introduction to the whole range of dental techniques, are obliged to spend their time on simple routine tasks, so repetitive as soon to blunt the edge of enthusiasm, and given little opportunity to exercise their medical knowledge, is appallingly wasteful. It is the kind of gross waste of skill and knowledge that goes too often unrecognised but which is none the less quite inexcusable. It can only be avoided by passing the routine work to ancillary workers, as is the universal practice in the wider field of medicine.

SENIOR SCHOOL DENTAL SURGEON.

Medicine and the Law

Error in Blood-Transfusion

SOME vigorous comments were made at a recent inquest in York where a patient had died in hospital after an error in blood-transfusion.[1] The coroner spoke of everything having gone wrong that could go wrong on that particular day. The mistake was apparently made at 4.30 P.M. when the theatre nurses went to tea and were replaced by others. A nurse, he said, went into the theatre not knowing the name of the patient; before she had time to speak to the nurse from whom she was taking over, she was sent for blood. She went to the laboratory not knowing for whose blood she was going. A doctor opened the refrigerator and pointed to a bottle. The bottle was not checked and the wrong bottle was taken. The blood was of the wrong group.

Such a mistake, said the coroner, could be avoided. The blood-bank could be divided into proper groups with separate compartments for blood to be used that day and a special compartment with the patient's name for blood needed for a particular patient's operation.

Recording a verdict of death by misadventure, the coroner stated that he had not summoned a jury because no person showed negligence of such a high degree of culpability that the issue should be left to a jury to decide. It had been distasteful to him to put questions to eminent professional men in a way which suggested that they might have been at fault. "Everyone," he said, "has the greatest sympathy with them, but at the same time the rewards for professional service are such that a very high degree of capability and skill is required of them."

Barbiturates in Bulk

The dangers of patients being given liberal supplies of barbiturates, to which we have lately drawn attention,[2] were unhappily illustrated by two cases of suicide from phenobarbitone with which the Manchester city coroner dealt on April 9.[3]

Both suicides were men of about fifty who had been given a fortnight's supply of the drug; one had been prescribed 72 tablets some ten days before his death and was found unconscious with only 4 tablets left. Giving evidence at the inquest, a doctor said that in hospital it was usual to give phenobarbitone only under strict supervision. He suggested that for outpatients it might be better to hand the tablets to some responsible relative.

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[1] *Yorkshire Post*, April 10.
[2] Annotation, *Lancet*, Feb. 23, 1952, p. 406.
[3] See *Manchester Guardian*, April 10, 1952.

There is bound to be some risk when potentially dangerous drugs are taken home by suicidally disposed patients, but it is one which every doctor who prescribes barbiturates should constantly bear in mind. Even small doses may be hoarded by a patient bent on suicide; and here the only safeguard lies in alertness for signs of mental depression,[4] so that we do not attempt to palliate a serious condition by drugs which may present a fatal temptation to the patient.

Public Health

World Incidence of Poliomyelitis in 1951

THE World Health Organisation has added another report [5] to the valuable series dealing with the incidence of poliomyelitis throughout the world since the war.[6] This latest report deals with incidence during the year 1951 and with certain epidemiological features which seem to have been more in evidence since the war than before it.

In Europe incidence was, on the whole, lower in 1951 than in 1950; but Italy, Norway, the Netherlands, and Switzerland reported more cases than in 1950. Unfortunately no information is available about incidence in Albania, Bulgaria, Czechoslovakia, Hungary, Poland, Rumania, the Soviet Occupation Zone of Germany, or the U.S.S.R. In Italy the number of reported cases—2870—was larger than in any of the previous fifteen years except 1939 (6007). In Norway 1553 paralytic cases and 663 non-paralytic cases were reported. These were the highest figures for thirty-two years except 1941 (1793 paralytic). In the Netherlands more cases (568, mainly paralytic) were recorded than in the previous three years together (308). Incidence was, however, a little lower than in the previous bad years—1930, 1938, 1943, 1944, and 1947. In Switzerland 889 cases were reported—a high incidence, but one which was exceeded in 1936, 1937, 1941, 1944, and 1946.

In the United States incidence was lower than in 1949 or 1950, while in Canada it was higher than in 1948 and 1950 but lower than in the other post-war years. In Mexico 1951 was the year of highest incidence since 1937.

Australia has suffered severely from poliomyelitis in recent years, and in 1951 notifications exceeded those of 1938 and 1950, which had been the years of highest incidence since 1924. In Oceania there were several scattered outbreaks—in the Solomon Islands, in Papua, in Dutch New Guinea, and in Tahiti. New Zealand had relatively few cases, in contrast to the experience of the years 1948–50.

In 1951 incidence was high in the Belgian Congo, in French Equatorial Africa, and in Angola. It is difficult to be sure whether these high reported incidences are due, in some measure, to better ascertainment; but the author is disposed to think that there has been a true increase.

Information about incidence in tropical countries is necessarily less complete than for Western countries, but a good deal of evidence is accumulating to show that some of the traditional generalisations about the epidemiology of poliomyelitis—e.g., that it is a disease of temperate climates with a high incidence in summer—may need drastic revision. The generalisation that epidemics arise at a definite season seems to be more true of countries with cold or temperate climates than of hot countries; but a good many winter epidemics have been recorded, and as far back as 1917 Leake et al.[7] collected some thirty examples. The report mentions the recent winter epidemics in Malta in 1942–43 and 1945–46 and in Iceland in 1946–47 and 1948–49, and the outbreak of 1948–49 among Eskimos living to the West of Hudson Bay.[8]

Vital Statistics for 1951

The Registrar-General [1] reports provisionally that in 1951 the birth-rate was 15·5 per 1000 home population; this rate was 0·3 below that for 1950. The provisional stillbirth-rate was 22·9 per 1000 total live and still births, compared with 22·7 in 1950. The death-rate was 12·5 per 1000 home population; this was 0·9 above that f 1950. Infant mortality was 29·6 per 1000 related li births, and was the lowest ever recorded in this countr The effective reproduction rate corresponding to t births in 1951, after making allowance for continui improvement in survivorship conditions, is provisional assessed at 0·97, indicating that births in 1951 were 3 below those required for a par replacement standard.

The Registrar-General also gives the followi abridged life table, constructed from the estimated hor population and total deaths in 1950:

Age x	Males		Females	
	A	B	A	B
0	10,000	66·49	10,000	71·22
1	9663	67·80	9740	72·11
2	9641	66·95	9718	71·28
3	9626	66·06	9706	70·36
4	9617	65·12	9697	69·43
5	9608	64·18	9689	68·49
10	9572	59·41	9664	63·66
15	9546	54·57	9645	58·78
20	9497	49·83	9607	54·00
25	9431	45·17	9554	49·29
30	9355	40·51	9489	44·61
35	9273	35·85	9416	39·93
40	9166	31·24	9324	35·30
45	9006	26·75	9201	30·74
50	8722	22·54	9005	26·35
55	8277	18·62	8722	22·13
60	7585	15·09	8307	17·11
65	6582	12·00	7676	14·39
70	5297	9·31	6729	11·07
75	3786	7·03	5359	8·26
80	2215	5·24	3584	6·11
85	939	3·95	1830	4·56

A = the numbers who would survive to exact age x out of 10,0(born who were subjected throughout their lives to the death pro abilities indicated by the 1950 death records. B = the "expectatic of life"—that is, the average future lifetime of someone exact x years of age, if likewise subject to these death probabilities.

Revised Regulations for Notification of Tuberculosis

The Public Health (Tuberculosis) Regulations, 195 which come into operation on May 1, replace those whic have been in force since 1930. There will be no chang so far as a notifying practitioner is concerned, but medical officer of health will no longer be required t keep a register of notifications, though he will doubtless continue to do so for his own purposes. It will no longer be legally necessary to provide information about a tuberculous patient entering or leaving a sanatorium or hospital, but the Minister has asked hospital boards and committees to ensure that this information is sent by the institution concerned to the medical officer of health of the district in which the patient lives.

Coöperation in Care of the Tuberculous

In a circular to hospital authorities (R.H.B.[52]30), the Ministry of Health refers to "lack of coöperation between chest clinics and Local Health Authorities which is impeding the Authorities in carrying out their responsibilities" for the prevention of tuberculosis and the care and aftercare of the tuberculous.

"It appears that, in particular, difficulty has been experienced by some Medical Officers of Health of Local Health Authorities in obtaining from Chest Physicians in charge of clinics the information required for the Authority's purposes contained in chest clinic registers or other case-records."

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[4] See Annotation, *Lancet*, 1951, ii, 1026.
[5] Freyche, M. J. *Epidem. vital Statist. Rep.* 1952, 5, 145.
[6] Stowman, K. *Ibid*, 1947, 1, 114. Freyche, M. J. *Ibid*, 1950, 3, 3. Freyche, M. J. *Ibid*, 1951, 4, 3.
[7] Leake, J. O., Bolten, J., Smith, H. F. *Publ. Hlth. Rep., Wash.* 1917, 32, 995.
[8] Peart, A. F. W. *Canad. J. publ. Hlth*, 1949, 40, 405.

[1] Registrar-General's Quarterly Return for England and Wales: Quarter ended Dec. 31, 1951. H.M. Stationery Office. Pp. 40. 2*s*. 6*d*.

"It has also been represented to the Minister," the circular continues, "that not all chest physicians are sufficiently concerning themselves in the preventive and after-care aspects of tuberculosis work."

Finally the circular recalls that the medical officer of health should be informed when patients with notifiable diseases, including tuberculosis, are admitted to, or discharged from, a sanatorium or hospital.

Variola Minor in South-east Lancashire

In the week ended April 19 notifications of variola minor in England numbered 2—one at Littleborough, a district already involved, and the other at Middleton, a borough close to Rochdale at which there has been no previous case. This patient sickened on April 13–14 and was removed to a smallpox hospital on April 17. Secondary spread is not expected.

The case notified from Wardle in the week ended April 12 was not smallpox. For the first time in nine weeks there were no notifications from Rochdale. Contacts are still under surveillance at Rochdale, Littleborough, and Middleton; but it seems possible that the outbreak has been contained. Notifications this year total 138.

At an inquest in Rochdale on April 14,[1] the coroner returned a verdict of death by misadventure in the case of a man, aged 26, who had died of encephalomyelitis twelve days after vaccination. According to medical evidence, 17,000 people had been vaccinated with the same batch of lymph without mishap.

Obituary

GEOFFREY BALMANNO FLEMING

M.B.E., M.D. Camb., LL.D. Glasg., F.R.C.P., F.R.F.P.S.

Dr. G. B. Fleming, emeritus professor of medical pædiatrics in the University of Glasgow, died on April 16 at the age of 69. His grandfather, who qualified in medicine in 1830, and his father were both surgeons at the Royal Infirmary, and his death thus brings to a close a span of three generations of his family who had practised in Glasgow.

He was educated at Haileybury, King's College, Cambridge, and Glasgow University. After taking his M.B. Camb. in 1910, he held resident posts in the Western Infirmary and Ruchill Fever Hospital in Glasgow. Later he spent some time in postgraduate study in Vienna, before he became assistant to the professor of medicine at Anderson's College, Glasgow. During the first world war he served in East Africa, with the rank of lieut.-colonel, and for his services he was appointed M.B.E. and mentioned in despatches. On his return to civilian life he became interested in pædiatrics and for 35 years he served on the staff of the Glasgow Royal Hospital for Sick Children at Yorkhill. In 1930 he succeeded Leonard Findlay in the chair of medical pædiatrics in the university. Under his guidance pædiatrics assumed a new importance for the medical student. A few years before his appointment tuition had been made compulsory, but largely by his efforts the time allotted to teaching was increased, and in 1935 pædiatrics became a part of the final examination in medicine.

During the '20s Fleming published important papers on basal metabolism and caloric requirements in infancy, and he earned an enviable reputation both at home and abroad. In his later years he became active in administration and committee work. In 1946 he was president of the British Pædiatric Association, and the same year he was elected to the presidency of the Royal Faculty of Physicians and Surgeons which his father had also held. He retired from his chair in 1947, and the same year under by-law xxxix(b) he was elected to the fellowship of the Royal College of Physicians of London.

"All who knew Fleming," writes S. G., "were impressed by his integrity and honesty. To work with him was to grow fond of him. He had an inborn courtesy which belonged to an earlier age and he was never heard to speak ill of anyone. He had many outside interests: he was a good shot and a good fisherman, and he played golf regularly. He loved, perhaps best of all, the company of congenial friends, when with good food and wine and engaging conversation he would radiate good cheer. Since last September he had faced ill health with simple faith and courage."

S. A. writes of the Dickensian quality of Fleming's appearance and personality. "The cut of his clothes, the festooned watch-chain, the oval lenses of his gold spectacles all helped to bring into sharper focus a picture of the traditional professor. Slight in build yet elegantly proportioned, he gave an impression of frailty, but his noble brow and benign expression provided reassuring testimony of health and mental alertness. These physical characteristics matured in the seventh decade of life, and his presence added an old-world charm to the precincts of hospital and university. They were seen to best advantage when after an informal dinner he indulged in the exquisite pleasure of proposing a toast. Wit and wisdom, nicely blended, flowed gently forth upon his delighted guests, who were till then rarely aware of the dialectic skill and resourcefulness of this diminutive and rather self-effacing physician.

"Naturally gentle and wont to show infinite consideration for the susceptibilities of others, he prided himself not so much on his attainments as on the honour of being a custodian of great traditions. Many of his apparently impromptu pronouncements on policy were in fact carefully prepared statements. He was by nature a thoughtful man; and he did not shrink from giving much of his leisure to the close examination of the changing circumstances of the practice of medicine. His memoranda were remarkable for comprehensiveness, a sense of reality, and excellent judgment. If he was generous of his time and energy, he was not less so with his material resources. He had inherited a large fortune and he elected not to take part in private practice. Both the university and the Royal Faculty have benefited from his munificence.

"He may not have shown great urgency in the pursuit of research; but his investigations on basal metabolism brought him recognition as an original worker. Moreover, he recognised the importance of investigation in maintaining freshness of outlook among the staff of a teaching hospital; and he did everything in his power to help young physicians and surgeons of his unit who had an aptitude for inquiry. He was, however, more than content to regard himself as essentially a practitioner-teacher, devoted to his young patients and anxious to expound to his students the practical approach of the competent family doctor. He will be remembered as a capable physician of the old school—shrewd and conscientious, gracious in manner, and generous to a fault. The Glasgow medical school has reason to be grateful to him for much unostentatious service performed with dignity and kindliness."

JOHN STROUD HOSFORD

F.R.C.S.E.

Mr. J. Stroud Hosford, consulting ophthalmic surgeon to the Royal Eye Hospital, London, died at Bexhill on April 10.

Born in 1872, he received his medical education at University College Hospital, London, where he qualified in 1895, and in 1904 he took the fellowship of the Royal College of Surgeons of Edinburgh. He also studied in Paris, Wiesbaden, and Vienna. Besides his appointment on the staff of the Royal Eye Hospital he had been dean of its medical school, and he was for many years surgeon to the London Temperance Hospital. His other appointments included those of ophthalmic surgeon to the Michie Military Hospital, Kensington, and to the Government medical board, Camberwell. He published papers on cerebellar tumour with proptosis, on the diagnosis of disease of the orbit, and on cataract.

C. writes: "Stroud Hosford had many interests besides ophthalmology. In his younger days he was fond of cycling, and almost every weekend he took his bicycle into Sussex where he studied, particularly, bird-life. He was keenly interested in astronomy, for the pursuit of which he had a small observatory built in his garden to house his 6 in. telescope. On one occasion he thought he had discovered a new star and telegraphed its position to the Astronomer Royal,

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1. *Manchester Guardian*, April 15.

who wired back that although the star was not a new one, to have seen it showed nevertheless fine powers of observation. After an illness in his early twenties Hosford was advised to take a sea trip, and as a surgeon in the P. & O. Company he visited India, China, and Japan. This voyage besides being beneficial to his health was of such interest that he later made another during which he met a learned Siamese doctor who was the means of consolidating and enlarging Hosford's interest, already formed, in Oriental philosophy, especially Buddhism. From then onwards till the end of his life his knowledge and understanding of this vast subject grew deeper, and in the course of years he formed what must be one of the finest collections of books on this subject in private hands."

Appointments

Ferguson, T. B., M.B. Glasg., D.P.H.: appointed to the staff of the regional M.O., Scottish region of British Railways, Glasgow.

Horton, E. H., M.B., B.SC. Wales, T.D.D.: deputy medical superintendent (S.H.M.O.), Glan Ely Hospital, Cardiff.

MacLeod, J. R., M.B. Leeds, M.RAD. Lpool, D.M.R.T.: consultant radiotherapist, United Leeds Hospitals.

MacQueen, I. A. G., M.D. Edin., D.P.H.: M.O.H., City of Aberdeen.

Mallender, Lilian, M.B. Leeds, D.M.R.T.: asst. radiotherapist (S.H.M.O.), United Leeds Hospitals.

Minto, W. H. P., M.B. Aberd., D.P.H.: M.O. on the staff of the County Council of Cornwall, asst. school M.O. and M.O.H., Area VI, Cornwall.

Ryan, O. P. D., M.B. N.U.I., M.R.C.P.I.: joint physician for the counties of Sligo, Leitrim, and Donegal.

Colonial Service

Behan, T. G., L.R.C.P.I.: M.O., Uganda.

Bennett, J. P., M.B. Durh.: M.O., Federation of Malaya.

Cathro, A. J. McG., M.B. St. And.: M.O., Kenya.

Chen, J. H., M.B. Hong-Kong, F.R.C.S.: M.O., Hong-Kong.

Cooper, P. R., M.B., D.T.M.: regional senior health officer, Nigeria.

Davey, T. F., O.B.E., M.D., M.SC. Manc.: leprosy adviser, Nigeria.

Ellis-Jones, D. W., M.B. Lpool, D.O.M.S.: ophthalmic specialist, Tanganyika.

Feanny, Lloyd, M.D. Dalhousie: M.O., Sarawak.

Forbes-Winslow, V. F., M.R.C.S., D.P.H.: regional senior health officer, Nigeria.

Golledge, A. H., M.R.C.S.: port health officer, Aden.

Kinsella, F. J. G., L.R.C.P.E.: M.O., Somaliland Protectorate.

Mitchell, R. M., M.B. Glasg., F.R.F.P.S.: special-grade M.O., Nyasaland.

Moore, William, M.B. Belf.: M.O., Uganda.

Peacock, J. G., M.R.C.S., D.A.: special-grade M.O., Tanganyika.

Seale, W. B., M.B. Dubl.: M.O., Uganda.

Sexton, J. P., M.B. Edin.: regional senior health officer, Nigeria.

Sinha, A. C., L.M.S. Singapore, M.R.C.O.G.: specialist officer, Federation of Malaya.

Slattery, M. F. X., M.D. Dubl.: M.O., Federation of Malaya.

Liverpool Regional Hospital Board:

Brown, D. P., M.B. Glasg., D.A.: part-time consultant anæsthetist to hospitals in the Southport and Ormskirk groups.

Downham, E. T., M.B. Lpool, D.P.M.: whole-time asst. psychiatrist, Walton Hospital.

Foody, J. T., M.B. N.U.I.: whole-time senior M.O., Barrowmore Hospital.

Hughes, Gough, M.B. Lpool, D.A.: part-time consultant anæsthetist to hospitals in the Central Wirral and Chester groups.

Moore, John, B.A., M.B. Dubl., D.A.: part-time anæsthetist to hospitals in Liverpool.

Murphy, A. F., M.CH. Lpool, F.R.C.S.: whole-time consultant general surgeon to hospitals in the North Liverpool group.

Rickham, P. P., M.S. Lond., F.R.C.S., D.C.H.: consultant pædiatric surgeon, Alder Hey Children's Hospital.

Skene, Alexander, M.B.E., M.B. Edin., M.R.C.P.: whole-time consultant physician-superintendent, Walton Hospital.

The Hospital for Sick Children, Great Ormond Street, London:

Hugh-Jones, Kenneth, M.D. Lond., M.R.C.P.: house-physician.

O'Donnell, M. B. N. J., F.R.C.S.: house-surgeon.

Patterson, T. J. S., M.B. Camb., F.R.C.S.: part-time registrar, plastic department.

Roberts, A. P., M.B. Lond., M.R.C.P., D.C.H.: house-physician.

University College Hospital of the West Indies:

Bunjé, H. W., M.D. Lond., M.R.C.P.: registrar.

Degazon, D. W., M.B. Lond., F.R.C.S.E., D.O.M.S.: consultant specialist in ophthalmology.

Jacobson, F. W., M.D. Berlin, L.R.C.P.E.: consultant specialist in dermatology.

James, Oliver, M.D. Lond: registrar.

Keating, V. J., M.B. N.U.I., lieut.-colonel R.A.M.C.: anæsthetist.

Ross, H. J., M.B. Aberd., F.R.C.S.: registrar.

Stuart, K. L., M.B. Belf.: registrar.

Sugar, Max, M.D.: consultant specialist in dermatology.

The Terms and Conditions of Service of Hospital Medical and Dental Staff apply to all N.H.S. hospital posts we advertise, unless otherwise stated. Canvassing disqualifies, but candidates may normally visit the hospital by appointment.

Notes and News

NEW MEDICAL RELIEF PLANS

An international conference on rehabilitation, held under the auspices of the World Veterans' Federation, opened in Paris on April 16. Delegates considered how modern methods of reablement could be extended for the benefit of disabled people in all countries.

Dr. Harold Balme, chairman of the United Nations working party on rehabilitation, said in his opening address that the fitting of artificial limbs was unsatisfactory in many countries, and he urged governments to take control of the manufacture of artificial limbs to ensure that every limbless person got the right kind of prosthesis. The conference approved a plan for courses of instruction for orthopædic surgeons and limb-fitters and other technicians to be held at the Ministry of Pensions hospital at Roehampton.

Speaking during the session on the reablement of ex-Servicemen, Dr. Ludwig Guttmann, director of the spinal injuries centre at Stoke Mandeville, described the success achieved with new methods of treatment in such injuries. Patients whose lives had seemed hopeless were being helped to take their places as productive members of society.

A programme of international aid for disabled ex-Servicemen, sponsored jointly by the federation and the Coöperative for American Remittances to Europe (CARE), was officially launched at the conference.

Medical relief to the distressed areas of Asia and elsewhere will be accelerated by the agreement just concluded between CARE and the World Health Organisation. W.H.O. cannot buy expensive supplies for medical institutions, and the progress of its work has been repeatedly held up by lack of equipment and beds in hospitals and clinics. CARE will now enlist American public support to meet the most urgent needs and send the equipment to the places recommended by W.H.O. By this means iron-lung "banks" will be set up in Tokyo, Bangkok, and a place to be selected in the Middle East, and 15,000 kits for midwives will go to India and South-East Asia.

HEBERDEN ROUND

The Heberden Round was conducted by Sir Henry Cohen, president of the Heberden Society and professor of medicine in the University of Liverpool, at the Royal Infirmary, Liverpool, on April 18. Cases of the diffuse collagen diseases, which had been under investigation with cortisone and A.C.T.H., were demonstrated.

Four patients with disseminated lupus erythematosus had shown general improvement with A.C.T.H., but in at least one case the histology had remained unchanged. Dermatomyositis in a child was being controlled by a small dose of A.C.T.H. every few days. She had quickly relapsed after attempts to substitute cortisone to avoid injections. A woman with Sjögren's syndrome, including swollen and painful parotid glands, granulopenia, arthritis, and hepatitis, had responded satisfactorily to A.C.T.H., and her hepatic function had improved. A patient with temporal arteritis (proved by biopsy) had been given A.C.T.H., and intense bilateral headache was relieved.

Sir Henry Cohen later entertained members of the society to dinner at the Staff House of the University of Liverpool.

IRISH INTERNS

When the compulsory intern year is introduced, as it may be next year, deans throughout the country will be working out sums involving x final-year students and y resident jobs. If x is greater than y, what is the answer? Dr. R. A. Stoney, president of the Irish Medical Registration Council, and the Council's intern committee have been trying their hand at this piece of mathematics as it applies in Eire.[1] A Bill has been passed by the Dáil and the Senate which corresponds closely to the clauses about interns in the Medical Act which Parliament passed in 1950. It is expected that the appointed day will be Jan. 1, 1953, and that 330–340 medical students will qualify in Eire in the year following. But the best estimates of available internships show that there will be 60–70 new doctors without jobs. Foreigners, Dr. Stoney thinks, might reasonably be expected to go home for their postgraduate year, since they will probably return home to practise anyway. If only half of them did so in 1953 the deficit would fall to the more manageable figure of

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1. *Irish J. med. Sci.* April, 1952, p. 174.

20 or so. And these, he suggests, can find employment in England where the provisional figures for 1953 indicate a surplus of 200 posts.

The difficulty of numbers does not seem therefore to be a formidable one, but Dr. Stoney is also concerned about money. The Irish intern will get £150 a year and his keep, and the hospitals will have to find not less than £50,000 every year to meet the increase in salaries of resident doctors. There is as yet no definite plan about where this is to come from.

AUTOMATIC PROCESSING OF X-RAY FILMS

A UNIT for the automatic processing of X-ray films, a prototype of which has been in use for some time in the department of diagnostic radiology at Guy's Hospital, is now being manufactured.[1] Its purpose is to ensure standard dark-room conditions as free as possible from human error. The dark-room technician has only to unload the cassette, fix the film in a hanger, and place it in the developing tank; the rest follows automatically. The hanger starts from a fixed point in the tank and is carried along by two moving belts on each side. Its speed is such that it reaches the end of the tank after the proper time of 5 minutes. It then touches a microswitch which operates a lifting arm driven by compressed air. The hanger is carried over to the fixing tank and on the way passes through a spray of water instead of the usual rinsing tank. Having deposited its load in the fixer, the arm returns in readiness for the next film. The moving belts take up the hanger again and carry it through the fixing tank. Another lifting device then removes it, carries it over a light trap, and sends it on its way through the final washing tank which is outside the dark room.

Each morning the developer is suitably replenished according to the number of films processed the day before, as recorded by an automatic counter. A replenishing technique has been devised which ensures a satisfactory chemical consistency for at least 12 months without emptying the tank. Temperature control is provided which is adequate for cold and temperate climates, but a refrigeration unit can be added for tropical use. Thus the time, temperature, and chemistry of development are very closely regulated.

The unit at Guy's, originally experimental, is now an established feature of the department. It enables a high standard of radiography to be more easily maintained and it saves time and materials.

University of Bristol

At a recent examination for part II of the diploma in medical radiodiagnosis the following were successful:

D. C. R. Burrows, W. A. Copland, Lien Chuan Yew.

United Sheffield Hospitals

At the third annual general meeting of the United Sheffield Hospitals, held on April 17, Sir Cecil Wakeley, P.R.C.S., was the guest speaker, following Sir Ernest Rock Carling and Lord Moran who addressed the two previous meetings. Applications for seats exceeded those available in the City Hall. Mr. Albert Ballard, chairman of the board of governors, presenting the annual report, spoke of the factors that have restricted hospital progress under the National Health Service—including competition for building materials, international economic crises, and rearmament.

> "Fourthly," he said, "we were operating a new Act of Parliament which in the case of the teaching hospitals was in danger of breaking an age-long tradition of voluntary service and which was to be coördinated and supervised by a Civil Service not too familiar with those traditions and in some cases antagonistic to the methods."

Nevertheless remarkable progress had been made in various ways, and the United Sheffield Hospitals last year treated 25,600 in their wards—an increase of 2780 over 1947. He concluded his review by saying:

> "Every social advance in this country expressed in an Act of Parliament begins as a compromise; is the result of debate and controversy, a concession here and an improvement there. Then in actual operation it is again criticised, again adapted to suit the area, period, or other circumstances. Never stereotyped, never ideal, never really logical. Therefore I am led to believe that our love of freedom, our tradition of tolerance, our insistence on variety, will save our great teaching hospitals from becoming merely Government departments so long as we continue to tap the immeasurable resources of good will, voluntary service, and idealism that have hitherto inspired us."

Royal College of Obstetricians and Gynæcologists

At a recent examination for the diploma in obstetrics the following were successful:

K. I'A. Alexander, A. C. Anderson, Elizabeth J. F. Anderson, Patricia Arnold, Herman Aufrichtig, H. M. Baird, John Barr, B. G. J. Barrett, M. M. Baskin, Arthur Bates, Margaret E. Beynon, J. P. Bingle, H. C. H. Bird, Margaret C. Black, Dorothy J. Blake, Olga Bolitho, John Breeze, V. R. Bruce, Peter Bryan-Brown, J. L. Butler, L. S. Calvert, D. M. Cameron, D. S. H. Cannon, Jack Cantor, E. F. Cassar, G. G. Champion, Shakuntla Prem Chandra, Gopal Vasudeo Chaphekar, Thin Mann Chin, J. M. Clarke, Gerald Clayton, A. W. Cook, Patricia B. Corston, Margaret J. Croall, H. E. Crosskey, D. M. Curtis, C. J. Davis, Esther M. Davis, Marie T. D'Netto, E. J. Fairlie, J. R. C. Flett, Agnes A. Flewett, T. S. Forsyth, William Fullerton, J. A. J. Geaghan, R. H. Gelb, G. L. Gleeson, Charles Gold, Ruth Y. Golder, John Gower, B. P. Green, A. C. Griffith, Brenda M. Grimmett, G. R. S. Grogono, Margaret E. Hall, Antoinette I. Hallett, R. P. C. Handfield-Jones, Geoffrey Hands, R. G. Hendrey, Muriel S. Hill, Ferdinand Hillman, Charles Hodes, M. McA. Holmes, M. F. Holt, P. T. Howse, Alexander Hunter, Nayma Hussain, A. F. M. Nural Islam, G. A. Jamieson, Nafra A. F. Johnston, A. J. Keane, Herbert Keidan, Aziz Ahmed Khattab, Malati Rajaram Khot, Alexander Kilpatrick, D. M. D. King, R. V. Knight, R. G. Krause, Satyendu Kumar Kundu, Anne M. Legge, Martin Lesser, G. P. Love, Alicja A. Lubicz-Sawicka, R. W. Lyle, Alexander Macdonald, A. D. Macdonald, Mary E. McGavin, R. A. McGregor, Patricia C. Mackay, W. T. Mackie, A. G. McKnight, Sheila C. McNally, Sushil Mallick, Lorna D. Malloch, Margaret B. Malloch, Peter Manolis, J. P. Masterton, Leela Menon, M. C. Michelow, Marion C. Miller, William Moore, A. D. Muirhead, P. H. Mulhern, G. J. Pack, Dharmarau Patnaik, A. B. L. Peake, J. K. P. Perera, Joan K. Perkins, B. W. Petty, D. L. Phillips, Margaret Pugh, Dulcie G. Rayment, Alison M. Richardson, E. J. E. Roche-Kelly, G. J. Rockley, Esmé S. Rogers, Irene H. Rogers, J. H. Ross, Anthony Ryle, J. R. Saunders, Audrey Seddon, Zubaida Khatoon Shaikh, H. G. I. Shanks, Kusum Kumari Sharma, J. B. Smith, M. H. Southall, J. T. Spenser, I. W. Stoddart, Evelyn Swangren, R. T. Swinburn, Frank Taylor, P. R. Thompson, Anne G. Tighe, Sushila Prabhaker Udani, W. H. Watson, Sheila M. Watts, N. W. F. Weir, Sheila M. E. West, A. J. White, V. T. White, D. J. Wilson, M. E. York-Moore, Bozena K. B. Ziolkowska.

The Leverhulme Foundation have given the college a further grant of £3000 for research in obstetrics and gynæcology.

Royal Institute of Public Health

The Harben medal has been awarded to Prof. E. C. Dodds, F.R.S., and the Smith award to Dr. Andrew Shinnie, medical officer of health for Westminster.

Hospital for Sick Children, Great Ormond Street

The centenary celebrations of this hospital are being held in London at the end of May. On May 27 the Princess Royal will lay a commemoration stone at the hospital, and there will also be a thanksgiving service at St. Martin-in-the-Fields. On May 26 there will be a programme of clinical demonstrations, and on May 29 the hospital will be open to past members of the medical, nursing, and lay staffs.

Ion Exchange Resins

The Physical Methods Group of the Society of Public Analysts and Other Analytical Chemists will discuss this subject at their meeting in Swansea on Friday, May 16. The speakers will include Prof. C. W. Davies, D.SC., Mr. G. H. Osborn, F.R.I.C., and Dr. F. W. Cornish, A.R.I.C. Further particulars may be had from the secretary, Mr. R. A. C. Isbell, A.INST.P., Hilger & Watts, Ltd., Hilger Division, 98, St. Pancras Way, London, N.W.1.

New M.R.C. Unit

The Medical Research Council has established a Unit for Research on the Experimental Pathology of the Skin, under the direction of Prof. J. R. Squire at the department of experimental pathology, Birmingham University. The Council's unit at the Birmingham Accident Hospital will now be known as the Industrial Injuries and Burns Research Unit and will be directed by Dr. J. P. Bull, who was formerly the assistant director.

Council for the Coördination of International Congresses of Medical Sciences

At the second general assembly, held in Geneva, under the chairmanship of Prof. Maurice Visscher (Minnesota University), it was decided to modify the title of the council, which will in future be known as the Council for International Organizations of Medical Sciences (CIOMS). The statutes of the council were also amended to increase the scope of its work. The executive committee was asked to explore methods for the integration on an international level of the indexing and abstracting of medical and biological literature "to render them more complete, more prompt and less expensive to the subscriber."

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[1] The manufacturers are Nucleonic and Radiological Developments Ltd., 22, Marshgate Lane, London, E.15.

Royal Appointments

Surgeon Rear-Admiral R. W. Mussen, C.B.E., F.R.C.P., has been appointed honorary physician to the Queen, and Surgeon Rear-Admiral James Hamilton, C.B.E., honorary surgeon to the Queen.

Gresham College, London

On April 28, 29, 30, and May 1, Prof. H. Hartridge, F.R.S., will deliver four lectures at the college. His subject will be the Physiology of the Blood. Further particulars will be found in our advertisement columns.

Welsh Board of Health

The Minister of Health has appointed Mr. H. H. Davies, M.C., to be chairman of the board in succession to Captain Geoffrey Crawshay. Mr. Davies, who is an assistant secretary at the Ministry of Housing and Local Government, was on the staff of the Ministry of Health from 1921 to 1951.

International Congress in Italy

An international medical congress is to be held from Oct. 16 to 18 at Montecatini, an Italian spa, to discuss contemporary medical problems. Further particulars may be had from the secretariat of the Congrès Mondial des Médecins pour l'Étude des Conditions Actuelles de Vie, Corso Trieste, 65, Rome.

EMERGENCY BED SERVICE.—In the week ended last Monday applications for general acute cases numbered 970. The proportion admitted was 91·6%.

CORRIGENDA: *Peripheral Neuritis.*—In this annotation last week (p. 806) the reference to the work of C. D. Aring should have appeared as *Brain*, 1942, 65, 34.

Medical Register.—The price of the Medical Register for 1952 is 42*s.* (43*s.* post free) and not as stated in our note of April 12. It is obtainable from Constable & Co. Ltd., 10, Orange Street, W.C.1.

Dr. E. R. Boland is visiting Yugoslavia to lecture for the British Council on the organisation of medical training in Great Britain.

Births, Marriages, and Deaths

BIRTHS

BARRINGTON.—On April 13, the wife of Dr. Rupert Barrington, of Haverhill, Suffolk—a son.

BUCKLEY.—On April 9, at Nottingham, the wife of Dr. John Buckley—a son.

CHASE.—On April 10, at West Kirby, the wife of Dr. W. H. Chase—a daughter.

COX.—On April 12, the wife of Dr. Patrick Cox—a son.

ELLIOT-SMITH.—On April 9, at Oxford, the wife of Mr. A. Elliot-Smith, F.R.C.S.—a son.

NAUGHTON.—On April 8, in Edinburgh, the wife of Dr. J. A. L. Naughton—a daughter.

RIDDELL.—On April 9, in Edinburgh, the wife of Dr. Michael Riddell—a son.

SCOTT WARREN.—On April 15, the wife of Dr. David Scott Warren, of Martley, near Worcester—a son.

WILLIAMS.—On April 12, at Ipswich, the wife of Dr. J. R. D. Williams—a son.

MARRIAGES

DAVIDSON—DUNN.—On April 19, at Arbroath, Samuel Lovell Davidson, F.R.C.S.E., to Harriet Elizabeth Marjory Dunn.

GUYMER—BIDSTRUP.—On April 18, in London, Ronald Frank (John) Guymer, M.D., to Patricia Lesley Bidstrup, M.R.C.P.

JOHNSTONE—WHITCOMBE.—On April 19, at Corstorphine, Edinburgh, Robert Douglas Johnstone, M.B., to Barbara Ann Whitcombe.

LAIDLAW—MAIR.—On April 2, at Port Glasgow, Allan James Laidlaw, L.R.C.P.E., of Worcester, to Greta MacAskill Mair, S.R.N.

PRESTON—TIBBS.—On April 19, at Lynchmere, Peter John Preston, M.R.C.S., surgeon lieutenant, R.N., to Margaret Ann Tibbs.

DEATHS

CHENNELL.—On April 16, Eileen Annie Chennell, M.B. Lond., D.P.M.

DEAS.—On April 17, at Bournemouth, Leonard Joseph Montagu Deas, F.R.C.S.E., colonel, I.M.S. retd, aged 78.

FLEMING.—On April 16, in Glasgow, Geoffrey Balmanno Fleming, M.B.E., M.D. Camb., LL.D. Glasg., F.R.C.P., F.R.F.P.S.

GOWANS.—On April 16, Francis Jollie Gowans, C.B., M.B. Durh., surgeon rear-admiral, aged 71.

HARE.—On April 16, John Hare, O.B.E., M.D. Durh., colonel, R.A.M.C. retd, of Chelsea.

JOHNSON.—On April 12, at Westcliff-on-Sea, Henry Johnson, L.M.S.S.A., F.F.A. R.C.S.

LEDGARD.—On April 11, at Windsor, Herbert Arthur (George) Ledgard, M.B. Leeds, surgeon lieut.-colonel, Royal Horse Guards.

Diary of the Week

APRIL 27 TO MAY 3

Sunday, 27th

LONDON JEWISH HOSPITAL MEDICAL SOCIETY
3 P.M. (Woburn House, Upper Woburn Place, W.C.1.) Arnold Sorsby: Genetics in Medicine.

Monday, 28th

ROYAL COLLEGE OF SURGEONS, Lincoln's Inn Fields, W.C.2
5.15 P.M. Prof. A. M. Boyd: Lymphœdema of the L Extremeties.
6.30 P.M. Prof. V. W. Dix: Ureteric Obstruction.
INSTITUTE OF DENT [illegible] Road, W.C.1
5 P.M. Dr. Frod [illegible]: Periodontitis Gingivitis a [illegible] nd Other Head
ROYAL SOCIETY OF [illegible] Street, W.1
5.30 P.M. *Section* [illegible] Neil Jenkins: Lal [illegible] of Fluorine to D [illegible] District.
ROYAL E [illegible] ge's Circus, S.E.1
5 P.M. [illegible]: Clinical Aspects of Accomn [illegible] Hypermetrope.
INSTITUTE OF PSYCHIATRY, Mau [illegible]
5.30 P.M. Dr. E. Stengel: [illegible]
MEDICAL SOCIETY OF LONDON.
8.30 P.M. Mr. W. W. Galbraith and Mr. J. G. Yates: Tuberculosis of Urinary Tract.
MANCHESTER MEDICAL SOCIETY
9 P.M. (University of Manchester.) *Section of General Pra* Dr. A. Morgan Jones: Treatment of Heart-failure.

Tuesday, 29th

ROYAL COLLEGE OF SURGEONS
5.15 P.M. Prof. Ian Aird: Peripheral Vascular Disease.
6.30 P.M. Prof. T. Pomfret Kilner: Cleft Lip and Palate
UNIVERSITY OF LONDON
5.30 P.M. (University College, Gower Street, W.C.1.) Prof. Hebb (McGill): Development of Perception and Tho (First of three lectures.)
ROYAL EYE HOSPITAL
5 P.M. Professor Sorsby: Genetics in Ophthalmology.

Wednesday, 30th

ROYAL COLLEGE OF SURGEONS
5.45 P.M. Mr. Harold Edwards: Abdominal Emergenci Childhood.
ROYAL EYE HOSPITAL
5.30 P.M. Mr. L. H. Savin: Proptosis.
ROYAL INSTITUTE OF PUBLIC HEALTH AND HYGIENE, 28, Por Place, W.1
3.30 P.M. Dr. S. Cochrane Shanks: Radiology and its tribution in the Diagnosis of Abdominal Disease.
MIDDLESEX COUNTY MEDICAL SOCIETY
3 P.M. (Shenley Hospital, near St. Albans, Hertfordshire.) S. T. Hayward: Psycho-analysis.

Thursday, 1st

ROYAL COLLEGE OF SURGEONS
5.30 P.M. Dr. H. A. Lucas: Histopathology of Sinusitis.
ROYAL SOCIETY, Burlington House, W.1
10.30 A.M. Prof. W. T. Astbury, F.R.S.: Structure of Prot
ROYAL EYE HOSPITAL
5.30 P.M. Miss J. M. Dollar: Surgery of Squint.
ST. [illegible]
5 [illegible]
WE [illegible]
5. [illegible]
INST [illegible]
5. [illegible]
UNIVERSITY OF DURHAM
5.15 P.M. (Royal Victoria Infirmary, Newcastle upon Dr. E. N. Cook: Hæmaturia. (Rutherford Morison lo
HONYMAN GILLESPIE LECTURE
5 P.M. (University New Buildings, Edinburgh.) Mr. I. Lawson Dick: Treatment of Dorso-lumbar Fract the Spine with Paraplegia.
UNIVERSITY OF ST. ANDREWS
5 P.M. (Medical School, Small's Wynd, Dundee.) P Whitteridge: Pathological Physiology of Dyspnœ

Friday, 2nd

ROYAL COLLEGE OF SURGEONS
5.15 P.M. Prof. B. W. Windeyer: Indications for Radioth
6.30 P.M. Sir Archibald McIndoe: Surgery of Repair.
ROYAL SOCIETY OF MEDICINE
10.30 A.M. *Section of Otology.* Prof. J. M. Robson, Prof Ormerod, Miss E. M. Whetnall, Dr. H. A. Luca A. S. Walker, Mr. Terence Cawthorne: Toxic Eff Streptomycin and Dihydrostreptomycin on the A and Vestibular Systems.
ROYAL EYE HOSPITAL
5.30 P.M. Dr. C. A. Keele: Physiology of A.C.T.H. and C with Special Reference to the Eye.
ROYAL INSTITUTION, 21, Albemarle Street, W.1
9 P.M. Prof. W. D. Wright, D.SC.: Defective Colour-visi
INSTITUTE OF DERMATOLOGY
5.30 P.M. Dr. R. M. B. MacKenna: Common Dermatose
INSTITUTE OF NEUROLOGY, National Hospital, Queen Square
5 P.M. Dr. R. Ollerenshaw: Technique of Illustrating Papers and Lectures.

Saturday, 3rd

INSTITUTE OF LARYNGOLOGY AND OTOLOGY, 330, Gray's Inn W.C.1
11.30 A.M. Prof. S. Podvinec (Zagreb): Physiology and -logy of the Soft Palate.

St. Robert Ewing Library
[illegible] Medical College